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DEPARTMENT OF REVIEWS

The Journal will make an especial feature of the review of monographs and books bearing upon the field of Internal Medicine. Authors and publishers wishing to subject such material for the purposes of review should send it to the editor. While obviously impossible to make extended reviews of all material, an acknowledgment of all matter sent will be made in the department of reviews.

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Cancer and Heredity*

MAUD SLYE, *Chicago, Illinois*

From the Otho S. A. Sprague Memorial Institute and the University of Chicago.

THERE are two aspects of this work that I wish especially to stress at this time. First I wish to show with what complete accuracy problems in the relation of heredity to disease can be worked out; second, to emphasize how great a need there is that this relation of heredity to disease should be thoroughly worked out for man, and to suggest the almost incalculable value such studies would have for the future of preventive medicine. Indeed, as I see it, they would revolutionize preventive medicine.

Almost nowhere in the field of scientific research have the findings been so entirely ignored as have been the findings regarding the relation of heredity to disease. During the past thirty years, there have appeared from various research laboratories, suggestions more or less definite that there was a relation between heredity and the occurrence of cancer in experimental animals, the tests being made for the most part with experimentally induced cancer, mainly grafted cancer.

For the past nineteen years I have been making an exhaustive study of this problem of the relation of heredity to predisposition to cancer and exemption from cancer, with all its related problems dealing with the nature and the minutiae of behavior of malignant diseases. Mice were selected for the work for the following reasons: they are mammals and the disease problems they present closely approximate human disease problems. They are small and a sufficient number of them to furnish conclusive evidence can be maintained without an excessive budget. Also very many generations can be studied in the lifetime of one worker. Most important of all their cancers are almost identical with those of man in type, in the organs involved, and in clinical course and behavior.

The malignant growths which this stock has furnished have included practically every type and location known in human pathology and the stock has also yielded many cases of leukemia, both myelogenous and lymphatic; of pseudoleukemia and lymphosarcoma.

All conclusions have been based upon numbers so large as to be beyond all possibility of coincidence and to allow a very wide margin for possible error. The numbers involved are to date over 67,000 necropsies, including between 5,000 and 6,000 primary spontaneous neoplasms.

*Presented before the American College of Physicians, March 5, 1928, New Orleans, La.

These cancers are not caused by any experimental procedure, as are the tar cancers, the grafted cancers, the cancers arising after infesting the animals with large numbers of parasite larvae, or any other experimental method. They are spontaneous cancers, arising in the natural life of the animals, exactly as man's spontaneous cancers arise. Thus there is no chance in the study of spontaneous tumors of involving any unconsidered quantities not present in human cancer, as may possibly be done in all experimentally induced tumors. The relation which heredity has seemed to bear to the occurrence of all of these spontaneous tumors has been consistently identical.

Searching tests have been carried out which conclusively show that cancer is not contagious in my stocks of mice. Every mouse is allowed to live out his full span of life, and to die a natural death. The clinical course of cancer is closely studied throughout the life of the animal in every case where the tumor can be diagnosed during life. Necropsy is performed as quickly as possible after death, and all suspicious tissues are microscopically examined.

The Inheritability of the Cancer Tendency.—The methods of studying the relation of heredity to the occurrence of spontaneous cancer in the laboratory have been the same as those which would be followed in studying intensively the inheritability of any character whatever, and the criterion of the inheritance behavior of cancer has been identical with the most rigid criterion that could be applied in any study of heredity.

In 1865 Mendel worked out with garden peas a study of the method of heredity. Later Cuenot and others working with mice, found that the mendelian method applied also in the inheritance of the animal characters tested. Throughout these studies hereditary predisposition has been shown to bear a definite relation both to the tendency to be exempt from cancer and the tendency to be susceptible to it. In thousands of mice bred in the laboratory, the tendency to be exempt from spontaneous cancer was transmitted as a simple dominant character along mendelian lines.

Results of cross breeding.—When a cancer-free mouse was mated with a cancerous mouse, none of the first generation offspring had cancer. The tendency to be exempt from cancer thus behaved like a simple mendelian dominant. If however, two of these first generation hybrids were mated, one-fourth of their offspring were susceptible to cancer, while three-fourths were exempt from it. Thus the tendency to be susceptible to cancer behaved like a simple mendelian recessive. If, instead of mating two first generation hybrids, each first generation hybrid was mated with a cancer-free mouse, no cancer appeared in the second generation. In this manner, that is by mating all first-generation hybrids with cancer-free mice, all cancer susceptibility has been ruled out of the entire family for many generations.

The tendency to be susceptible to cancer is also inheritable, but it is inheritable as a recessive character. This means, that even though there has been a great deal of cancer in one side of

the family, even 100%, if there is no cancer in the other side of the family, all of the immediate progeny have been cancer free. If they in their turn have been mated with cancer resistant individuals, cancer has been eliminated from their immediate families also.

By the successive mating of dominant non-cancerous mice with hybrid non-cancerous mice, cancer has been held off indefinitely but has still been present potentially, transmitted by the hybrid carrier through generation after generation, but never frankly shown as long as dominant non-cancer is mated with hybrid carriers. But when, in any generation, the 2nd, the 3rd, the nth, two hybrid non-cancerous mice have been mated, cancer has appeared in the next generation in almost mendelian ratio where the mice have lived well into cancer age. In the studies in this laboratory cancer has been held off for twenty-five generations by persistently mating analyzed dominant non-cancer with hybrid carriers through successive generations. But when eventually two of these hybrid carriers were mated, cancer has appeared in the next generation.

It is this possibility of transmitting cancer through successive generations by the right selective mating, without its frank appearance which would explain in human statistics the seemingly erratic occurrence of cancer sometimes in a family where no previous case has been known. Our human statistics however usually cover only two ancestral generations and the diagnoses in these were rarely based upon necropsy.

Out of the many hundreds of tests made in this laboratory a few typical ones have been selected and charted here to show both the method of procedure and the kind of results obtained. Note how exactly these results follow the mendelian expectation in heredity from the given type of cross made, and how rigid is the method of analysis by which the mice are classified in regard to their cancer tendency.

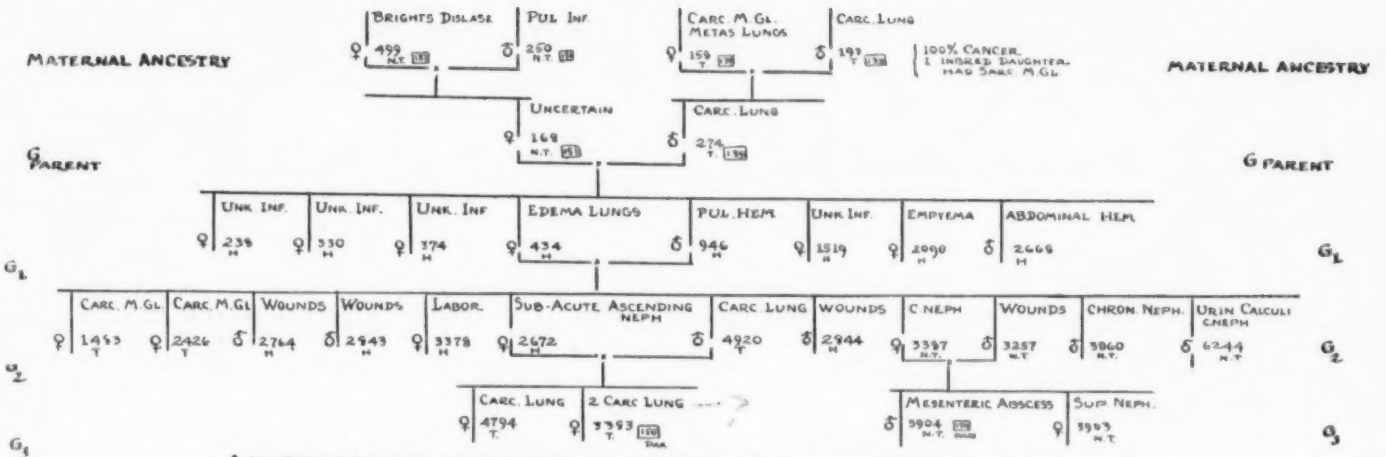
In this strain the parent female was 168. She was the daughter of parents neither of which had cancer. Her mother, female 499, died in old age of chronic nephritis; and her father, male 250, died of pulmonary infection. Female 168 herself died of uncertain causes but had no tumor. She had therefore been selected for this cross as she apparently was an extracted non-tumorous mouse.

The parent male 274 died of carcinoma of the lung. He came of a family which showed at necropsy 100% of cancer (strain 139). His mother 158, died of carcinoma of the mammary gland with metastases in the lungs; his father 193, with primary carcinoma of the lung. He was therefore used in this cross because he was an analyzed extracted cancerous individual.

We have here then a typical mendelian cross between the presence and the absence of a character: that is female 168 with the cancer-resistant tendency present and male 274 with the cancer-resistant tendency absent. The first hybrid generation showed no cancer whatever, which is the typical behavior in hybridization for a mendelian recessive. *The non-cancer tendency then was dominant over the cancer tendency in this cross,* just as pigmentation was dominant over the absence of

STRAIN 145

(ORIG. ♀ × ♂ STRAIN 151 / 139)



A MATING BETWEEN AN ANALYZED NON-TUMOROUS ♀ WITH A TUMOROUS ♂ GIVING PERFECT MENDELIAN RESULTS, SHOWING CANCER BEHAVING AS A SIMPLE MENDELIAN RECESSIVE.

CHART I

pigmentation in the standard mendelian diagram. When two of these first generation hybrid non cancerous mice were mated, (female 434 who died with edema of the lungs without cancer, and male 946 who died of pulmonary hemorrhage without cancer) the resulting offspring showed the nearly perfect mendelian ratio of four dominant non-cancer, to six hybrid non-cancer to three recessive cancer mice. The cancer representatives were females 1483 and 2426 with carcinoma of the mammary gland, and male 4920 with a carcinoma of the lung.

Female 2672, in the second generation, who died of subacute ascending nephritis, was analyzed to determine whether she was dominant non-cancer or hybrid non-cancer, by being mated with male 4920 with cancer of the lung. Cancer appeared in her immediate offspring; female 4794 with carcinoma of the lung, and female 3383 with two primary carcinomas of the mammary gland. Female 2672 was thus shown to be a hybrid non-cancerous mouse capable of transmitting the disease though not herself frankly showing it. This mating also demonstrated the fact that when hybrid non-cancer is mated with recessive cancer, cancer appears in the immediate offspring, just as recessive albinism appears in the immediate offspring in the similar classic cross.

In the effort to derive an analyzed extracted dominant non-cancerous mouse, two others of the offspring of the same first generation hybrid carriers were selected, namely female 3387 who died of chronic nephritis without cancer, and male 3257 who died of wounds without cancer. Their son, male 3904, shown in this chart, who died of a mesenteric abscess without tumor, and their daughter, female 3903, dying of suppurative nephritis without cancer, appeared to be extracted dominant non-cancerous mice.

As all these mice were autopsied as are all others dying in this laboratory, and as every suspicious tissue is examined microscopically, it is absolutely known which mice have and which have not any form of neoplasm.

By this cross then there was obtained an analyzed cancerous female 3383 and an analyzed extracted non-cancerous male 3904 for further testing. Note that the types of tumors which appeared in this strain 145, and the organs in which they were located, were identical with those bred in, namely carcinoma of the mammary gland from ancestral female 158, and carcinoma of the lung from ancestral male 193 and parent male 274. Moreover no other types or locations of neoplasms occurred in this family.

Ancestral male 193 had one daughter in strain 139 (from which he was derived) with sarcoma of the mammary gland. Sarcoma of the mammary gland came out later in strain 145 as shown in chart 4, thus proving male 193 a hybrid carrier of sarcoma of the mammary gland as well as carcinoma of the mammary gland, though not himself frankly showing either, as he died with carcinoma of the lung.

The inheritance behavior then of the cancer-resistant tendency and the cancer-susceptible tendency are here identical with the pigmentation tendency and the non-pigmentation tendency. The cancer resistant tendency like the pigmentation tendency behaved like a

mendelian dominant, and the cancer-susceptible tendency, like the non-pigmentation tendency, behaved like a recessive. Also, just as the type of color bred in is the one which appears in the offspring, so the types and locations of neoplasms bred in, were the ones which occurred in the offspring.

Chart 2 shows the inbred test which was given male 3904 to prove whether he was certainly an extracted pure bred cancer-resistant mouse. He was mated with his sister female 3903 (also shown in chart 1). She died of suppurative nephritis without tumor and appeared also to be an extracted pure-bred cancer-resistant mouse as did all other mice in this branch. No fraternity of this branch of strain 145 has ever shown a neoplasm either malignant or benign, although the strain still persists in the laboratory and has been in existence for over seventeen years, the original cross having been made in October, 1910. We have here then analyzed pure-bred cancer-resistant mice for hybridization testing.

To further test male 3904 as an extracted dominant non-cancerous mouse, he was hybridized with absolutely unrelated female 711 who was an analyzed non-cancerous member of strain 71 and who died in old age of an aortic rupture without tumor. No fraternity of this strain 224 ever showed a neoplasm malignant or benign, although it persisted in the laboratory for five years.

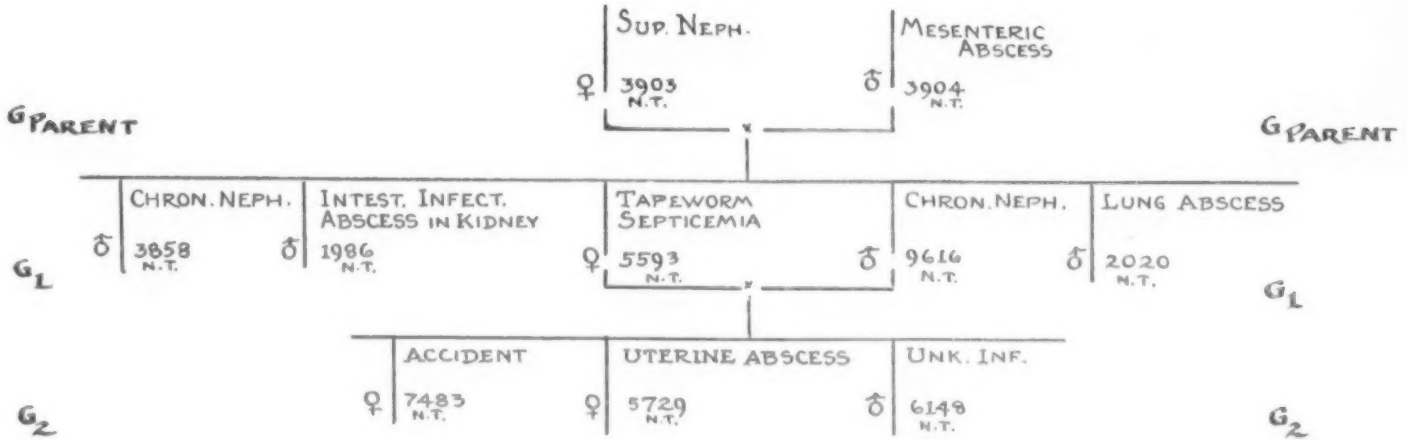
This is the method by which are analyzed all mice appearing in these studies. They are not chance mice picked up in the market or in the laboratory and mated by chance. They are analyzed individuals whose ancestry and inheritance potentialities are known facts and they can therefore be manipulated with a certain outcome.

Chart 4 shows a part of strain 150 which resulted from the cross of analyzed cancerous female 3383 and analyzed cancer-resistant male 3904. The first hybrid generation from this cross was all non-cancerous, that is, again the non-cancer tendency was dominant over the cancer tendency; but cancer appeared in the second generation in female 9778 with a carcinoma of the mammary gland, and male 5696 with a sarcoma of the mammary gland. Again when cancerous male 5695 was mated with non-cancerous female 5786, no cancer appeared in the next generation. In both tests then shown in this chart the non-cancer tendency was dominant over the cancer tendency.

This chart shows also the origins of Branches I, II, III, and IV of this strain. Branch I is made by the crossing of two *first generation* hybrids, female 6488 and male 5426. Branch II is derived from mating two other *first generation* hybrids, female 10852 and male 8035. Branch III is made by mating two hybrid non-cancerous mice, of the *second generation* female 12148 and male 11246. Branch IV is derived by mating two *second generation* extracted dominant non-cancerous mice, female 10911 and male 11346. Note how in every case the inheritance behavior is in exact accord with the standard mendelian expectation. That is, (1) the mating of a cancerous and a dominant non-cancerous mouse gives hybrid non-cancerous mice, with cancer appearing in the second generation. (2) The mating of two hybrid non-cancerous mice gives the standard three

PART OF STRAIN 145

INBRED ANALYSIS OF ♂ 3904 PROVING HIM NON-TUMOROUS



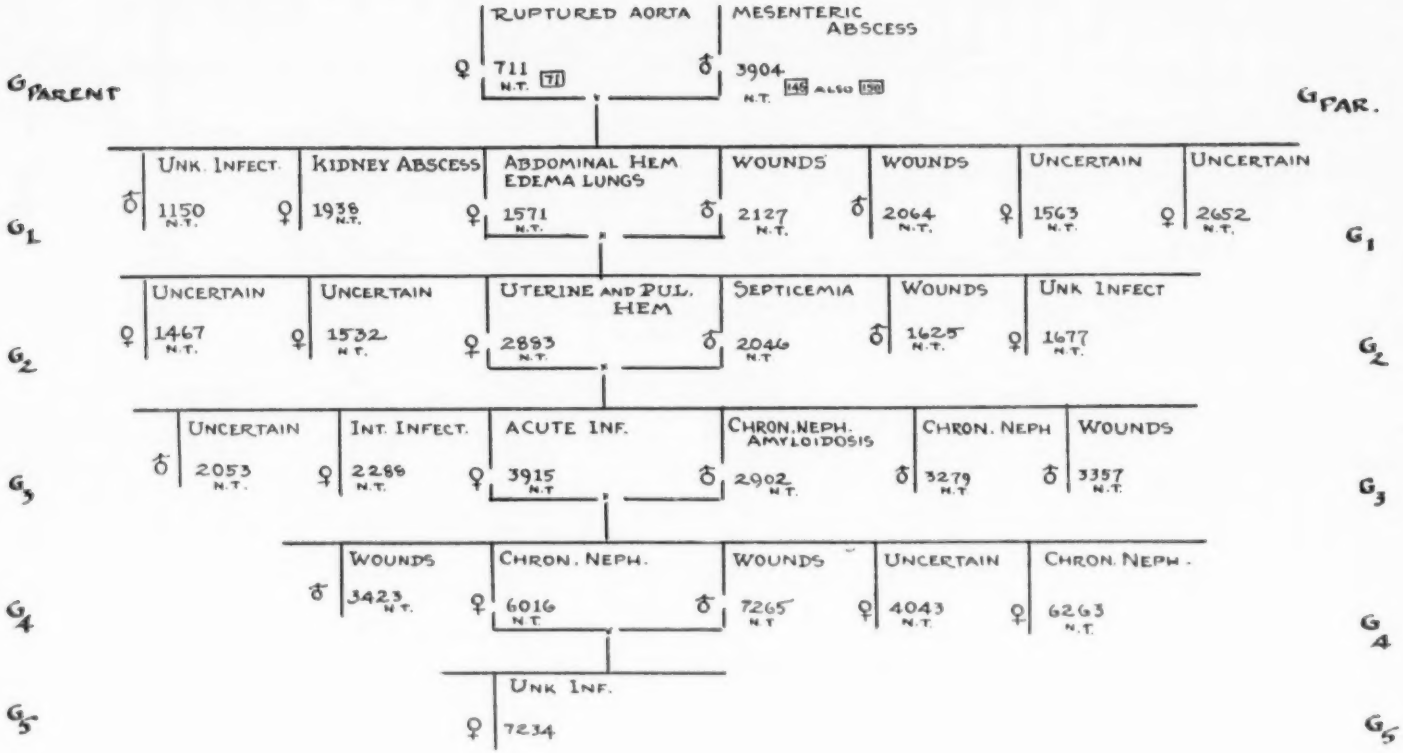
NO FRATERNITY IN THIS BRANCH OF THE FAMILY EVER PRODUCED A NEOPLASM EITHER MALIGNANT OR BENIGN.

CHART 2

STRAIN 224

OUTBRED ANALYSIS OF ♂ 3904 PROVING HIM NON-TUMOROUS

[X BETWEEN ♀ STRAIN 71 / ♂ " 145]



NO FRATERNITY IN THIS FAMILY EVER PRODUCED A TUMOR MALIGNANT OR BENIGN.

CHART 3

PART OF STRAIN 150

SHOWING MATING OF ANALYZED NON-TUMOROUS ♂ 3904 WITH CARCINOMATOUS ♀3383

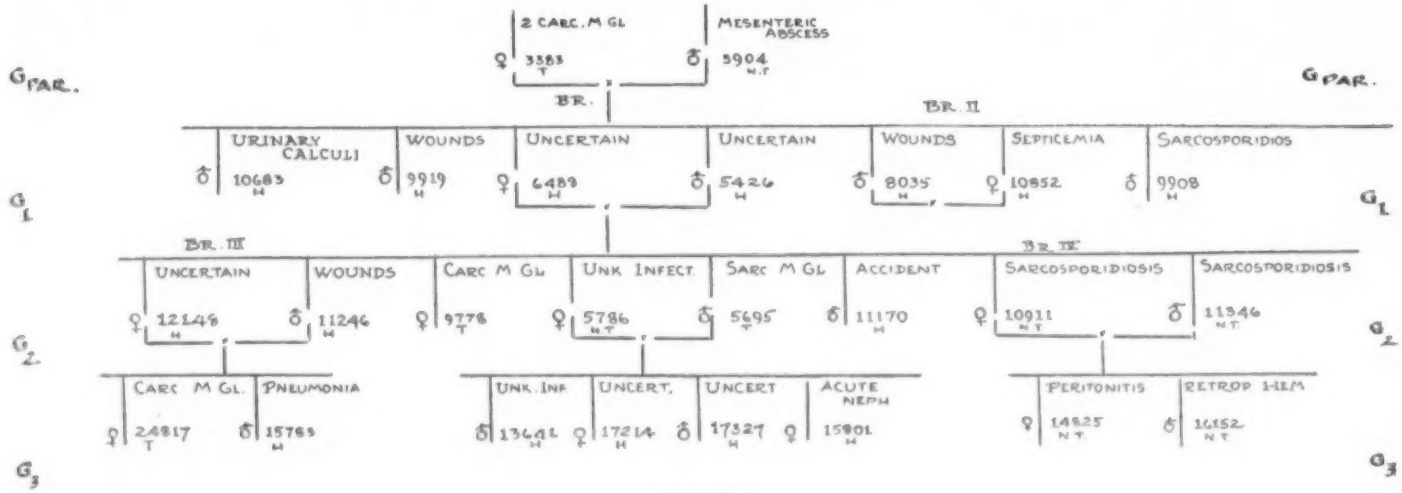


CHART 4

types, dominant non-cancer, hybrid non-cancer and recessive cancer. (3) The mating of two dominant non-cancerous mice gives extracted non-cancer only, no cancer ever appearing again in such branches.

Chart 5 gives the continuation of Branch I and shows the result of mating analyzed dominant non-tumorous female 5786 with her cancerous brother 5695 both of the second generation shown in chart 4. None of their immediate offspring ever showed tumor of any nature. Cancer thus again behaved like a recessive. Note that four branches of this family were made by mating four pairs of these hybrid non-cancerous mice, and in every case some cancer appeared in the next generation (generation 4 in the chart).

Note that throughout these charts the only tumors, both primary and secondary, which occurred, were tumors of the mammary gland and of the lung, like the ancestral tumors of the strain shown in chart I.

Chart 6 shows part of an extracted 100% cancerous strain (strain 338 Br. V) derived from double cancerous parentage, female 8619 with two carcinomas of the mammary gland and male 8751 with an adenoma of the liver. The ancestry behind this strain has been published previously. (1) It is here omitted in order to get the chart within the necessary size limits. The ancestry while in my hands, carried sarcomas, carcinomas and adenomas in most of the organs here represented.

Note the large number of liver tumors, sarcomas and adenomas, there being eleven cases of liver tumor, primary and secondary, out of twenty-four individuals, or nearly 50%. This is very noteworthy, because outside of this laboratory there have been only two spontaneous liver tumors in mice reported in all the literature, one by the Imperial Cancer Research Laboratory of England, (2) and one from the cancer laboratory of Harvard University in Boston, Mass (3).

The liver tumors in this strain 338 were deliberately bred for, in the effort to show that the uncommon internal tumors, as well as the more common mammary gland tumors, unquestionably were determined by heredity.

In line A note female 8865 with an osteosarcoma of the mammary gland metastasizing in the liver, succeeded by her grandson male 16370 with an osteosarcoma of the subcutaneous tissues of the leg, metastasizing in the liver.

Note the very frequent occurrence in this strain of multiple tumors, particularly females 9741, 12261, 22263, 30469 and 30501. The latter two mice had more neoplastic than normal tissues at the time of their death.

In this strain there is one case of pseudoleukemia, a disease which also occurred in the ancestry of this strain. In this laboratory chronic leukemia, pseudoleukemia, lymphosarcoma and kindred diseases have uniformly occurred in cancer strains only, and have followed the laws of heredity as surely as have neoplastic diseases. Their behavior in this laboratory would indi-

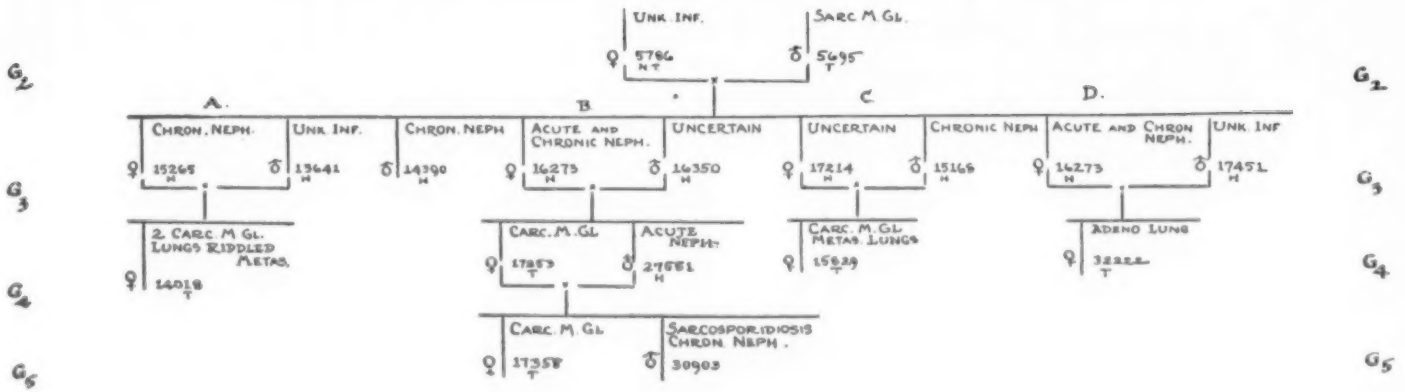
(1) Slye: Jour. Can. Res. Vol. I. No. 4. 1916.

(2) Murray: Third Scientific Report of the Imperial Cancer Research Fund, 1908, 69.

(3) Tyzzer: Jour. Med. Res. 1909, XXI, 479.

PART OF STRAIN 150 BR.I

CONTINUED ANALYSIS OF MATING OF CANCEROUS WITH NON-CANCEROUS MICE



A CROSS BETWEEN A NON-TUMOROUS FEMALE AND A TUMOROUS MALE SHOWING HOW CANCER APPEARED IN THE SECOND HYBRID GENERATION FROM EVERY TESTING OF FIRST GENERATION HYBRID-CARRIERS IN LINES A-B-C-D~

CHART 5

PART of STRAIN 338 BR.V

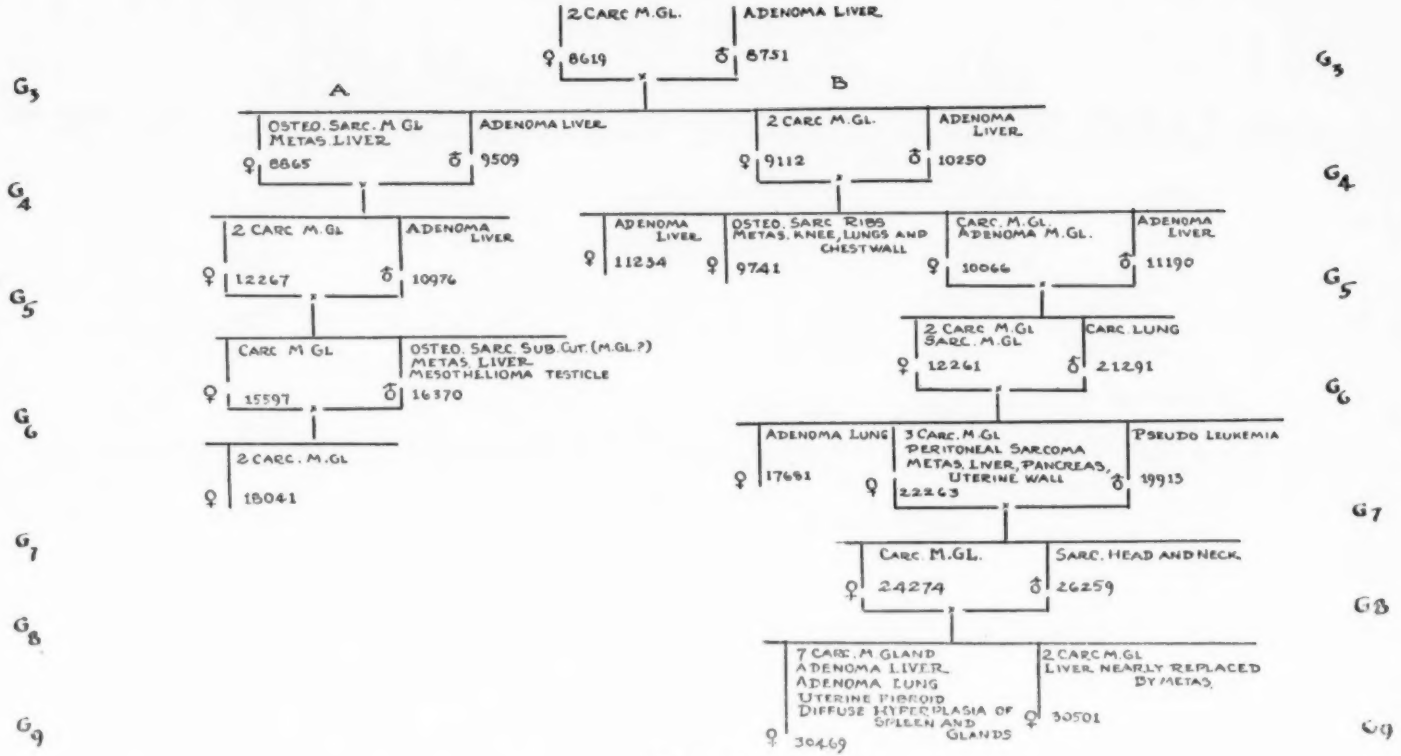


CHART 6

cate that they certainly are neoplastic diseases.

These charts are typical. Whenever in this laboratory two analyzed cancer-free mice have been mated, it has always been possible to secure 100% cancer-free families. In such crosses no instance of cancer in the succeeding strain has ever to date occurred. Also when two cancerous mice have been mated it has been possible to secure 100% cancer susceptible strains except for those mice that have died in infancy or that have been swept off by infections earlier in life than the normal age for the type of cancer to which they are predisposed. Occasionally a mouse in one of these 100% cancer strains derived from double cancerous parentage has developed a cancer when only two weeks old, although six months is an early cancer age in mice and is approximately the equivalent of about 32 years, an early cancer age in man.

In the hybridization test also susceptibility to cancer and exemption from cancer have uniformly proved to be inheritable. They have followed almost with exactness the standard expectation for a typical mendelian recessive and dominant respectively. Thus the tendency to exemption from cancer is unquestionably inheritable. Many hundreds of strains and branch strains have been carried in this laboratory, which have never shown a tumor growth of any kind. This means that in many families carried for fifty or more generations and comprising many thousands of members, there has been complete exemption from cancer. These cancer-free mice when bred into other families, carry with them exemption from cancer as a dominant character. Compare this with the record of man who pays no attention to heredity in his matings, and where one in eight over a given age is dying of cancer, and note how tremendously hopeful is this fact of the inheritability of the tendency to be exempt from cancer.

Even when a recessive cancer-susceptible mouse is mated with a hybrid carrier of the cancer tendency it is possible in the third generation to derive dominant pure breeding cancer-resistant individuals. This possibility of extracting wholly cancer-free families even where one parent was cancerous and the other is a cancer carrier is a most encouraging fact and it should be strongly emphasized. From every mating of a cancer-susceptible individual with a cancer-resistant individual, either dominant or hybrid, it has been possible by the right selective mating to produce families wholly resistant to cancer.

It is this hybridization test which proves beyond dispute the inheritability of any character, for nothing but heredity could explain the segregating out and the transmission unchanged of characters in which the two parents are unlike, and the perfect mendelian pattern which they follow: as for example, albinism and pigmentation, or cancer susceptibility and cancer resistance.

Where both parents die of the same disease and all the later members of the family die of the same cause, as in a 100% inbred test, we have no absolute demonstration that it might not be a case of epidemic contagion, either extra- or intra-uterine. But we cannot explain by contagion, the perfect men-

delian pattern shown in a hybridization test. This pattern by every test that can be made, the cancer-susceptible and the cancer-resistant tendencies in mice of my stocks have uniformly followed.

The Influence of Heredity in Determining Secondary Neoplasms.

Not only has heredity definitely controlled the occurrence of primary tumors, but it has also controlled the occurrence of secondary tumors. (4) The tests made in this laboratory have shown that the only secondary tumors which occur in any strain, correspond with the primary tumors within that strain, both in type and in the organs in which they occur; thus showing that only those organs susceptible by heredity to primary tumors in any individual or strain, are susceptible to secondary growths.

These tests have demonstrated also that secondary tumors are as potent as primary tumors in heredity, in determining the type and the location of primary neoplasms in mice. That is, for example, the tendency to primary sarcoma of the kidney has followed from an ancestor with secondary sarcoma of the kidney, and vice versa. Note chart 7.

Strains 48 and 292. The parents in these strains are female 3 and male 360. Female 3 had a sarcoma-carcinoma of the mammary gland, a malignant adenoma of the liver, and sarcoma metastases in the kidney. She came of a family (strain 90) which carried also tumors of the mesenteric glands, ovary, spleen, adrenal and lungs, as well as leukemia and pesudoleukemia. She proved to be a hybrid carrier of the tendency of these organs to be susceptible to cancer, as well as of the tendency to leukemia and pseudoleukemia, and she transmitted the tendency to tumors in all of these organs to some of her posterity in hybrid crosses with analyzed dominant non-tumorous mice. She also frankly showed mammary gland, liver and kidney neoplasms of both carcinoma and sarcoma types.

Parent male 360 was the son of male 436 who died of carcinoma of the lung. This strain also carried mediastinal tumors primary and secondary. Male 360 then, was a 1st generation hybrid carrier of tumors of the lung and mediastinum, although not frankly showing tumor.

We have here then the mating of a tumorous female with a hybrid-carrier male. The first hybrid generation from this cross showed some tumorous individuals and some hybrid carriers in about equal numbers.

Note that both the primary tumors and the secondary tumors are of the same types and occur in the same organs as those bred in.

These strains were selected because they show locations of neoplasms in mice which have not been reported at all or else rarely reported from other laboratories. This chart shows that these internal tumors, difficult to diagnose clinically, follow exactly the same laws of heredity as do the easily noted mammary gland and skin tumors.

It is very difficult and laborious to secure these strains yielding high percentages of internal tumors, because it is so difficult to diagnose them before the death of the mouse and in time to secure offspring from such a selected

(4) Slye: Jour. Can. Res. Vol. VI, No. 3, 1921.

PARTS OF STRAINS 48 AND 292

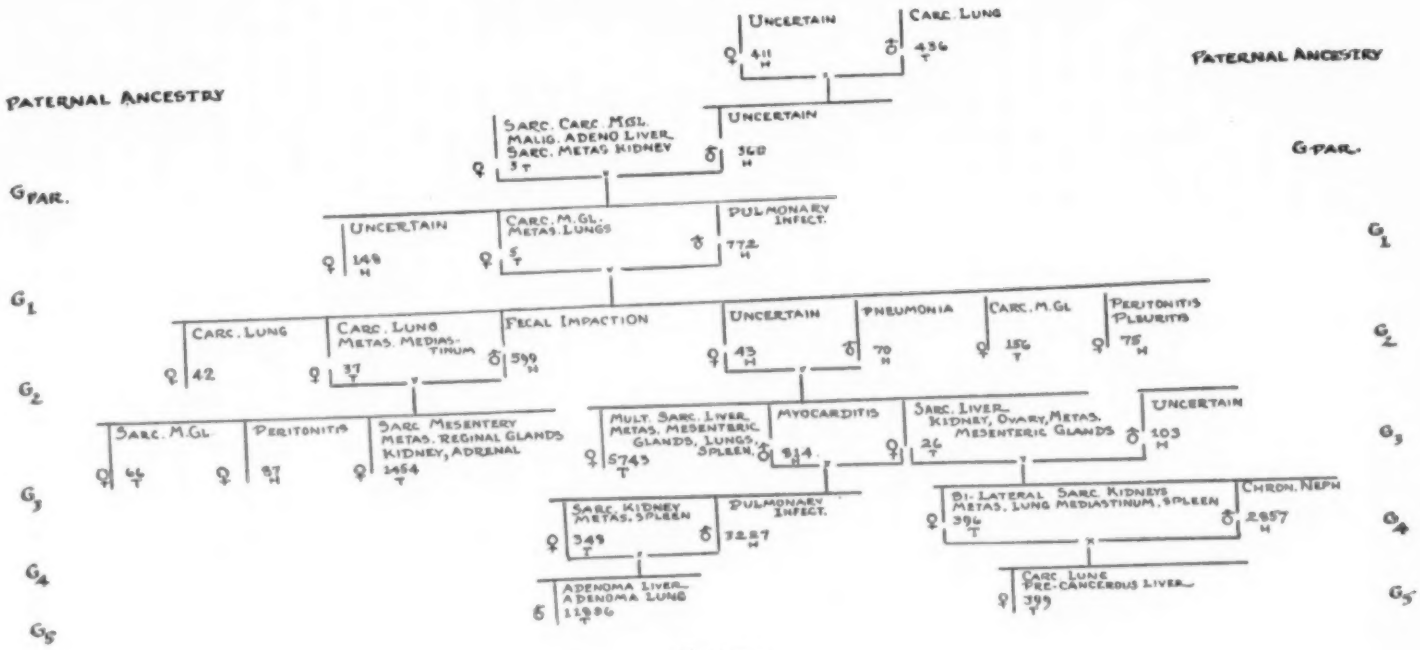


CHART 7

cancerous parentage. Only by long continued and painstaking effort is it possible to obtain them, but when we find 5 sarcomas of the kidney, 4 sarcomas of the liver, 3 sarcomas of the mesentery, 1 sarcoma of the adrenal, 3 sarcomas of the spleen, and 1 sarcoma of the ovary, in addition to numerous carcinomas of the mammary gland and lung, in a little family of sixteen members, whose ancestry was known to carry all these types of tumors, the certainty of heredity control is evident.

It has been suggested that mammary gland cancer being the most commonly reported tumor in mice, might occur by chance in these large numbers, but it is not possible to think that such rarely reported internal tumors as those shown in this typical chart, could have occurred in such numbers by chance.

Many strains in this laboratory (4) have been so manipulated in selective breeding as to exclude primary tumors of the lung, which are common tumors in mice. The lung is also one of the most frequently reported seats of secondary growths in mice. In such strains in my stocks where primary lung tumors never occur, no tumor metastases grow in the lungs even where tumor emboli are very numerous in the lung blood vessels.

Chart 8 shows a 100% lung tumor strain, strain 139. Every member of this family that lived to be six months of age or over, showed lung carcinoma either primary or secondary.

Chart 9 shows another lung tumor strain. Every member of this family except male 2501 had lung carcinoma either primary or secondary. Male 2501 had a testicular tumor only.

Chart 10 shows a part of strain 392. Note female 12058 of the fourth generation shown in the chart. If her statistics had been taken for three generations only no tumor would have been shown in the family. But if we examine one generation farther back we find almost the duplicate of the new growths shown in female 12058. This indicates how deceptive may be the results of an examination of the death causes in the ancestry for even three generations. It also indicates how the tendency to cancer persists in hybrid carriers through generation after generation, until the right mating is made; when the cancer tendency appears in the next generation.

Charts 11 and 12 show the almost perfect inheritance behavior of thyroid malignancy as a simple mendelian recessive, occurring in strain J. D. 30-62-68. The mating is between female 24843 with thyroid carcinoma, and non-cancerous male 24383. The first hybrid generation (gen. 15 in the chart) showed no tumor. No tumor appeared in the second hybrid generation, where it might have been expected; but all of these mice died rather early for the occurrence of thyroid malignancy. When two of the 16th generation mice were mated however, thyroid malignancy occurred in the next generation. Again in generation 18, from the mating of cancerous female 31909 with non-cancerous male 32556, no cancer occurred in the next generation. But when two of these hybrid carriers were mated, thyroid carcinoma occurred in the next generation, female

(4) Slye: Jour. Can. Res. Vol. VI, No. 2, 1921.

STRAIN 139

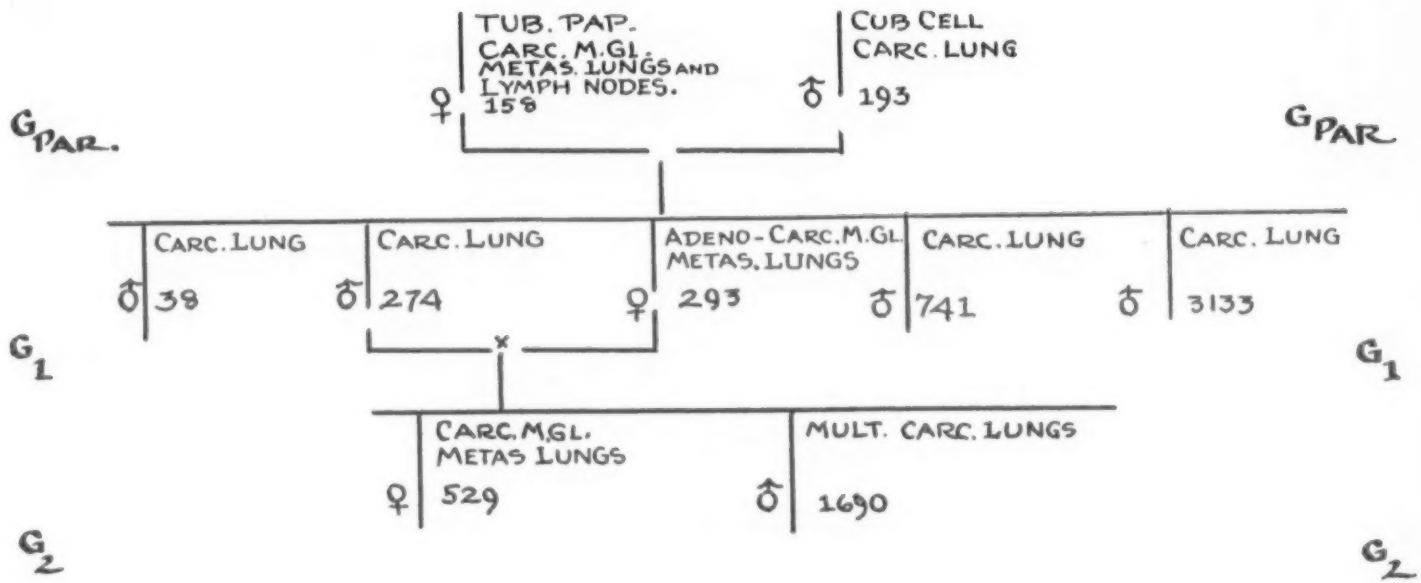


CHART 8

STRAIN 280

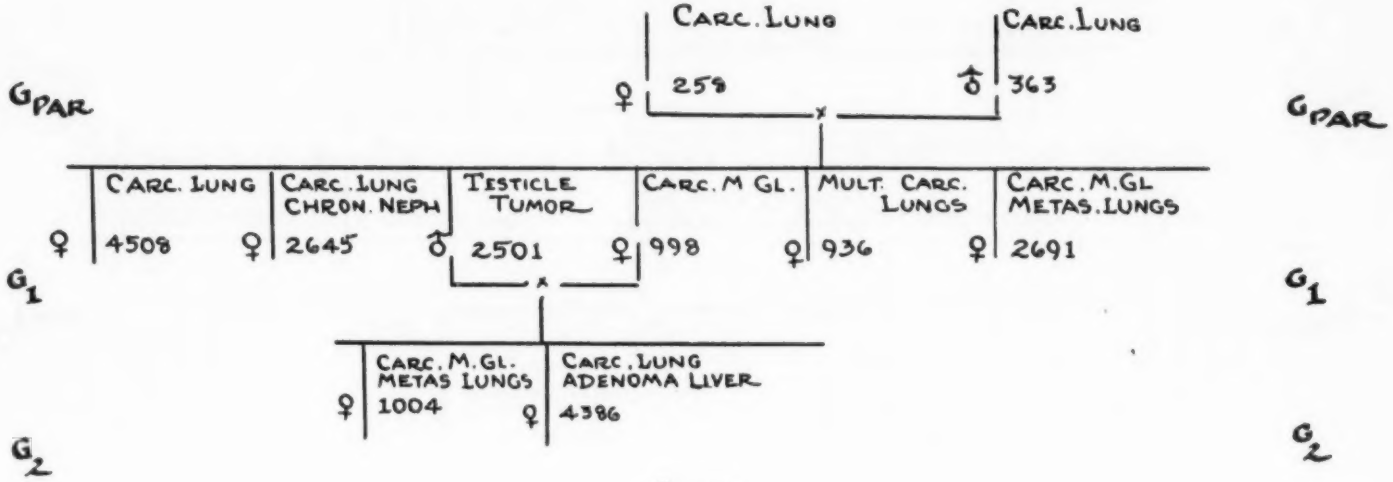


CHART 9

37841. When this female 37841 was mated with hybrid carrier male 35938, thyroid malignancy occurred in the next generation. This chart shows the almost perfect inheritance behavior of a given type and location of malig-

Chart 12 shows how by the continuous mating of a non-cancerous individual with a hybrid carrier in each successive generation of this same family after the 22nd generation, all malignancy was held off for five genera-

CHART 10

nancy, (that is sarcoma-carcinoma of the thyroid) as a simple mendelian recessive character. This is very striking, because thyroid malignancy in mice has nowhere else been reported. This classic occurrence of this type of tumor deliberately bred for in one family of mice, is noteworthy.

tions. The tendency however was still present in the family, transmitted by the hybrid carriers through generation after generation. When in the 27th generation two of these hybrid carriers were mated, sarcoma-carcinoma of the thyroid occurred again in the 28th generation. This is the most stringent

test that can be made to show whether or not any character has a hereditary basis. The occurrence of thyroid malignancy in the 28th generation of this family showed the perfect mendelian ratio of one-fourth cancer free, to two-fourths hybrid carrier, to one-fourth

cations. This branch of the family was chosen to show this particular type of proliferation. Other branches of the family showed malignancy in other locations, according to the matings made. In my experience, these pre-cancerous proliferations of muzzle skin and eye-

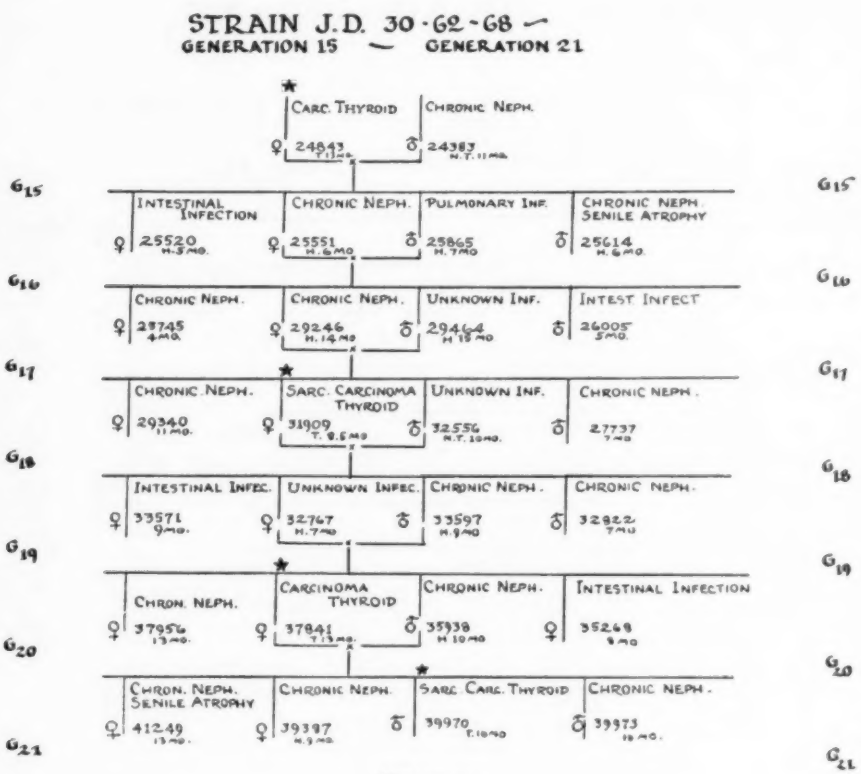


CHART 11

thyroid malignancy. Some of the non-tumorous members of the family are omitted, in order to get the chart within the necessary limits.

Chart 13 shows a family of strain 150 derived from the mating of two cancerous parents. Note the high percentage of basal-cell carcinoma of the eyelids and muzzle skin and pre-cancerous proliferation in these same lids have gone on to malignancy in every case where the mouse has lived long enough for this to occur.

Chart 14 shows two branches of strain 215. Note the high percentage of carcinoma and adenoma of the lung in branch A and the high percentage of liver adenomas in branch B (each according to the matings made). The frequency of liver tumors in branch B

STRAIN J.D. 30 - 62 - 68

GENERATION 21 — GENERATION 28

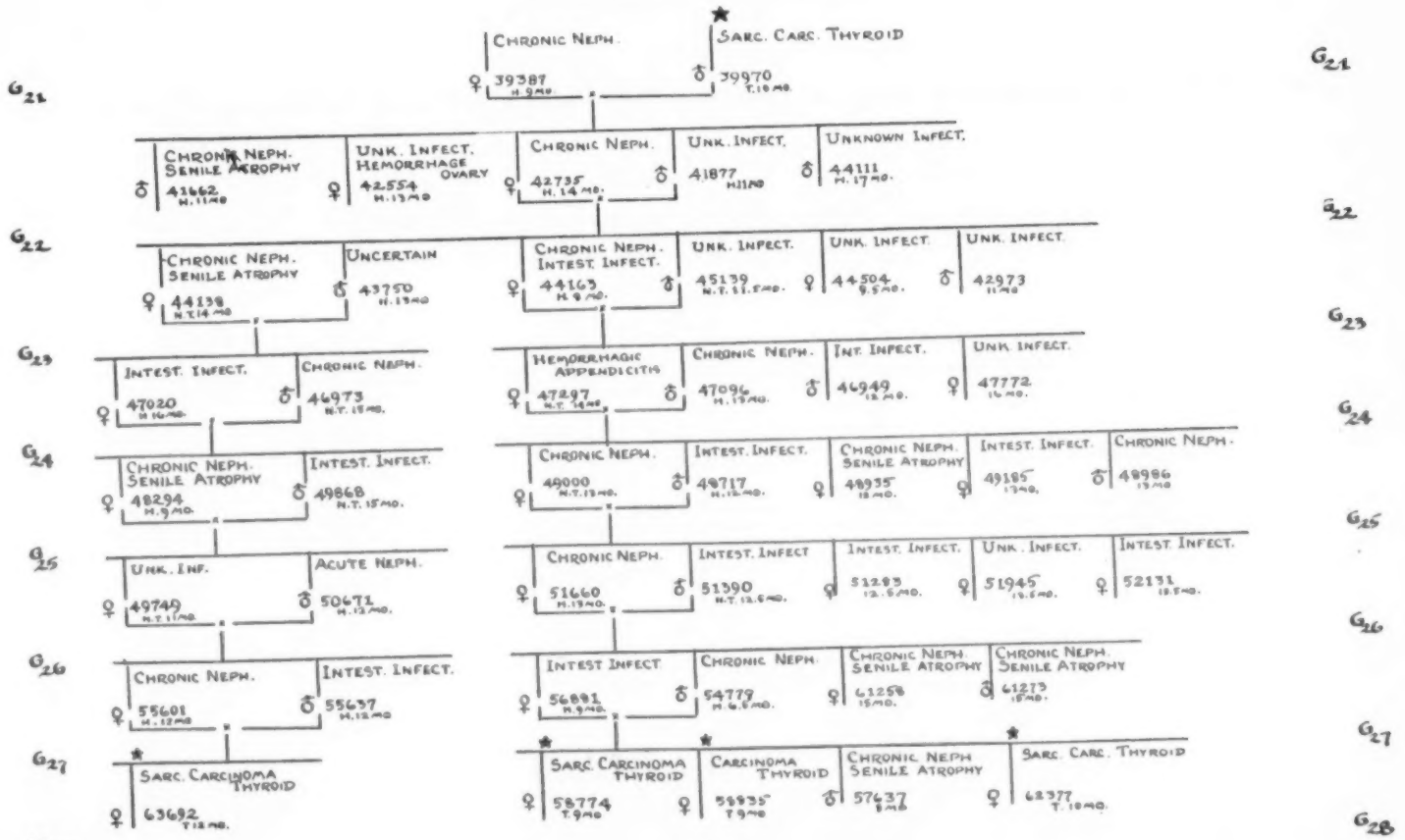
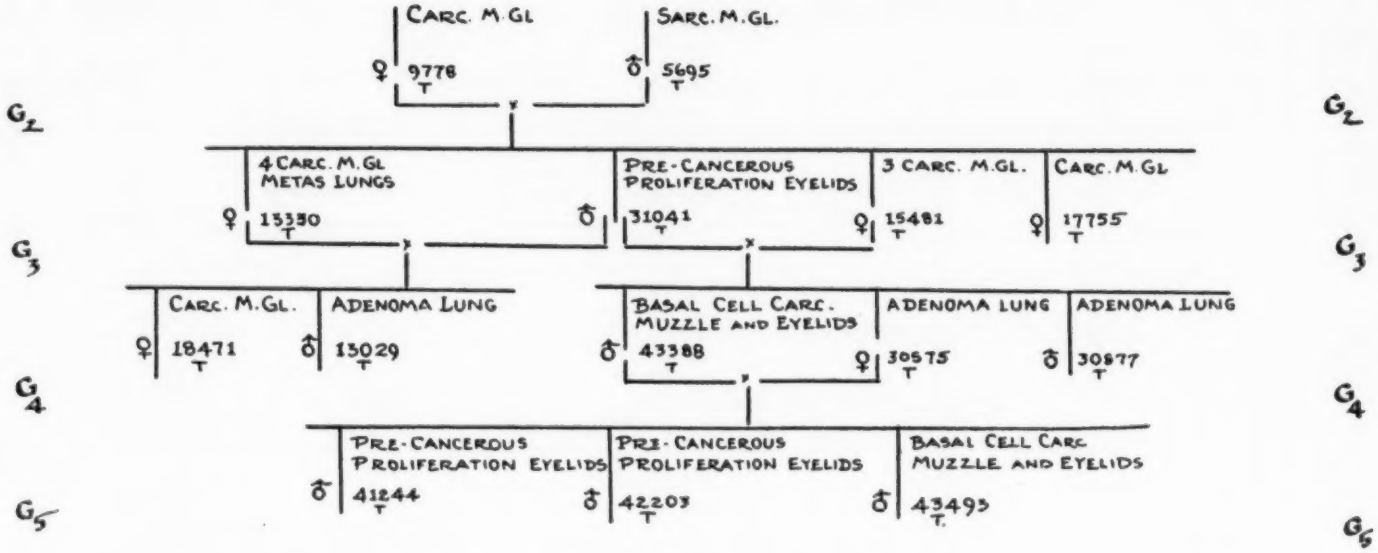


CHART 12

STRAIN 150 (PART 9)



A 100% TUMEROUS STRAIN FROM THE MATING OF TWO TUMOROUS PARENTS

CHART 13

PART OF STRAIN 215 AND SOME DERIVATIVES

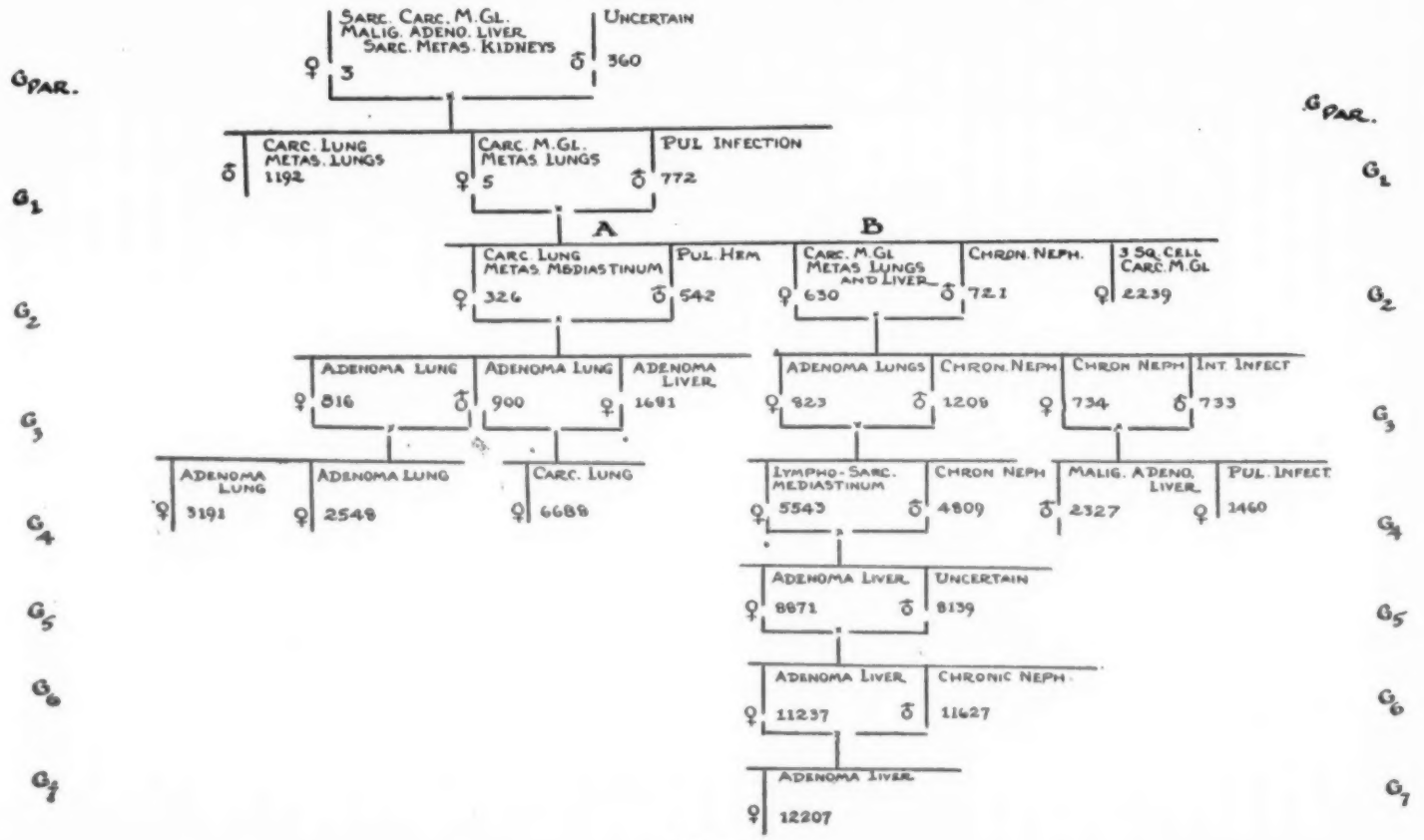


CHART 14

is very striking as this is a tumor very rarely reported. These were malignant adenomas.

In strains which do not carry liver tumors, no secondary growths have appeared in the liver, even when multiple emboli have been present throughout the liver vessels, whereas in those strains where primary liver tumors occur, the liver is a frequent site for secondary growths, as shown in strain 338 Br. C, in strains 48 and 292.

There are apparently two factors necessary to induce cancer. If either of them could be wholly avoided, it might be possible to prevent cancer. These factors are (1) an inherited local susceptibility to the disease, and (2) irritation of the appropriate kind and the appropriate degree applied to the cancer-susceptible tissues. Experiments eliminating one or the other of these two factors, in order to see whether cancer can be avoided in this way, are being carried on in this laboratory with a promise of some success. In these experiments by avoiding either the cancer susceptible factor or the irritation factor, cancer has in some cases been avoided. The experiments thus suggest that both inherited susceptibility and local irritation are necessary in inducing cancer. They suggest that cancer susceptibility is local and not systemic. In mice susceptible to only one location of cancer, no amount of irritation or stimulation applied to other parts of the body has ever to date induced a cancer. Avoidance of irritation to the locally susceptible tissues has prevented cancer in some cases, even in susceptible individuals. This would suggest that if an individual susceptible to cancer will protect himself against irritation of locally susceptible tissues, he might avoid cancer even though he is a member of a family with much cancer.

The fact of the inheritability of exemption from cancer is one of the few hopeful observations ever made concerning the disease, because it means that instead of every one being susceptible, large numbers are wholly exempt. It also means that it is possible wholly to eliminate cancer from any family by the right genetic procedure, as I have eliminated it from hundreds of families involving thousands of individuals.

What I have said regarding the certainty of the relation of heredity to exemption from spontaneous cancer and to the tendency to be susceptible to cancer has to do with the mice of my stocks. Its application to man and to most other animals remains to be tried. But mice are mammals like man, organ for organ their anatomy and functions are markedly similar in all fundamentals which we can test.

We find marked similarity in such types of tissue behavior, both normal and abnormal, as we are able to study in man and the lower mammals. Tissue reactions in reproduction, regeneration and all the fundamental vital processes are markedly similar. The differences in refinements and complexities attach themselves only to the less basic entities.

The spontaneous cancers in mice are also similar to those of man in every essential of structure and of behavior of which we are informed. Heredity is the most fundamental of all basic biologic facts next to the fact of the existence of life itself, and it

plays the leading rôle in evolution, keeping species and even varieties pure. Heredity applies in man and it applies in mice. Man has neoplasms and mice have similar neoplasms. The suggestion that the relation between heredity and cancer must be similar in both, surely offers itself, unless we discard evolution as the explanation of organic life as it exists today. For if evolution means anything, it must mean that down the full line from the single cell to man, similar tissues derived from ancestral tissues have responded in the same way as the ancestral tissues to the same types of stimulation. Only so could an unbroken series of organisms evolve each from the preceding. The methods and facts of heredity in man would therefore seem to be similar to the methods and facts of heredity in mice, unless there is a break in the evolutionary series between man and all other forms of life, thus isolating him from every other form of life.

Therefore since it is possible wholly to eliminate spontaneous cancer from families of mice by the appropriate genetic procedure, it might prove to be possible so to eliminate cancer from families of man. This does not mean that we can relax our vigilance against any forms of chronic irritations in any case, since we have not as yet even begun to apply the facts of heredity to the human species, and we have few adequate statistics of human heredity in relation to disease. But it does mean that we should begin to get correct scientific human statistics regarding diseases in man, based upon operation, biopsy, or necropsy in every case, and not upon opinion, so that we could make such an application because in this procedure lies much hope.

Moreover since there is in man the beginning of a genetic sense, (that is a sense for the fitness of matings) it should be possible to educate this genetic sense. This is the great hope for humanity. The way to educate it is to make generally known the facts and operation of heredity, so that man need not be blind as to what characters he is transmitting to his posterity. If, moreover, we would uniformly permit necropsy as is the invariable rule in this laboratory, the exact facts concerning diseases in man could be obtained. If these facts were then kept in permanent record in the laboratory, in two generations by the right selective matings it might prove to be possible to begin to eliminate cancer, as I have consistently and completely eliminated it from hundreds of families of mice in the laboratory.

I am aware that the problem of founding permanent correct human cancer archives is a difficult one as every great work is difficult, but it is largely for the purpose of presenting the necessity of such a foundation and to urge this society to begin it, that I am here.

Two generations of medical men will handle at least four generations of cancer patients. If we had a sufficient number of cases on record and available for study, four generations of accurate records would almost certainly give us the necessary data in each possible type of mating, to demonstrate the relation of heredity to cancer susceptibility and cancer exemption in man, or to prove that there is no such relation.

With all the experimental evidence which is now at hand on this subject of heredity, the time obviously has come when permanently available human records are the immediate requirement. The great mass of valuable human records which exists today, is, with a few notable exceptions like those of Warthin, Broca and some others, so buried in widely scattered masses of local data as to be unavailable.

If we would begin, each in his own location, to make duplicate permanent heredity records of every suspected cancer case, with duplicate permanent slides from operation, biopsy or necropsy in every case, the solution of the problem would be at hand. These duplicates, records and slides from every location should in every case be deposited in a central permanent bureau, where they can be studied together. That central bureau I greatly desire to see located in Chicago which is a central city, so that it would be possible for me to organize the data, and to begin to analyze it, thus starting the permanent foundation. Indeed I would receive it in the beginning in my own laboratory and carry on the necessary work of organization, until the permanent location should be established.

I have brought this matter before this body, because most cancer cases in their beginnings come to you. How you handle them largely determines the outcome. It lies within your possibility to keep track of them from the beginning to the end. It is easily within your power to begin such a foundation if it appeals to you as a necessary thing to be done, and I have therefore brought the matter first to you.

There is open to you now, in my opinion, the greatest opportunity for a tremendous advance in medical science that anywhere presents itself today, that is, the practical incorporation of the immeasurable benefits of the facts of heredity into future preventive medicine. Such an incorporation will revolutionize preventive medicine. If the time were at my disposal I would show you how.

I am here therefore to beg that a committee of your organization be appointed to consider ways and means by which permanent scientific human cancer archives can be founded. I promise you every co-operation of ideas and of service that lies within my power now and in the future. I also beg the local co-operation of every member of this great society toward this end.

For if the findings in regard to the relation of heredity to malignant diseases in mice should prove to hold for man, and every biologic fact at our disposal indicates that they would thus hold, and if we make our data available, for the first time in the history of the study of this disease, the way of the complete elimination of cancer is open.

Some Considerations Upon the Etiologic Agent in Yellow Fever*

By Aristides Agramonte, M.D. (*University of Havana, Cuba.*)

A Board of U. S. Army officers in 1900-1901 (1) discovered the manner in which mosquitoes transmit yellow fever from man to man, a theory announced and advocated by Dr. Carlos J. Finlay since 1881 (2).

The result of its investigations showed the following:

1. That soiled linen, bedding, etc. so-called "fomites" are absolutely non-infective; there is no direct contagion in yellow fever;

2. That the mosquito becomes infected only when it sucks blood from a patient during the first three days, possibly four days, of his illness;

3. That the mosquito becomes capable of transmitting the disease only after ten, possibly twelve, days of having sucked blood as above stated;

4. That once infected, the mosquito is capable of transmitting the disease throughout its life-time.

These findings have been corroborated by several Committees appointed for the purpose in Cuba, Brazil and Mexico.

*Presented before the American College of Physicians, March 5, 1928, New Orleans, La.

In taking into account the considerations that I am about to submit, it is important that we bear in mind the above facts, none of which can be any longer discussed; they have become almost axiomatic as far as the relations of yellow fever with mosquitoes or with "fomites" is concerned.

Now, in the course of the last half century, several yellow fever parasites have cropped up as the result of more or less (more often less) painstaking efforts on the part of enthusiastic investigators.

Of all these various germs, the *Bacillus icteroides* of Sanarelli (3) and the *Leptospira icteroides* of Noguchi, (4) enjoyed the greater period of credit. *Bacillus icteroides* has been discarded as having any relation with yellow fever since the Spanish-American War. Noguchi's *Leptospira* is of more recent origin and has been kept before the scientific world as the etiologic agent for the last eight years.

A cursory examination of Dr. Noguchi's claims reveals the following:

1. That *Leptospira* was obtained originally by injecting guniea-pigs with blood from yellow fever patients, the organism appearing then in the animals' blood, causing symptoms and le-

sions declared to be similar to those of yellow fever in man;

2. That the *Leptospira* infects guinea-pigs by contact and by injection into their tissues;

3. Young dogs become infected by feeding upon the *Leptospira;*

4. The *Leptospira* shows positive Pfeiffer reaction with yellow fever convalescent serum in about 90% of the tests;

5. Inocculation of animals by mosquitoes has given positive result in rare cases;

6. A vaccine and a serum have been prepared from this organism and injected as a prophylactic and a cure of yellow fever, respectively.

Several years' experience with yellow fever in the midst of severe epidemics and the fact of my connection with the work of the Army Board above referred to, induced me, from the very first articles of Dr. Noguchi to look upon his claims of specificity for the *Leptospira,* with much reticence, and a certain degree of incredulity; Noguchi's name constituted a trade-mark, (if you will allow the term), that offered unusual guarantee of excellent and thorough scientific research, just as Sanarelli's name did, in the case of his *Bacillus icteroides.*

Drs. Guiteras and Lebredo, well versed in the problems of yellow fever, both agreed with me in that some of the characteristics of the *Leptospira did not conform with what* must necessarily be characteristic of the yellow fever parasite, but still we awaited the further conclusive experimentation that was to be expected.

In the meantime, a culture of *L. icteroides* was graciously furnished by Dr. Noguchi to my colleague Dr. Lebredo, which after repeated plantings and inoculations upon various animals in various ways, (by mouth, subcutaneously, intraperitoneally and by contact), served to further convince us that such an almost saprophytic organism could not be the elusive yellow fever parasite. (5) The cultural characteristics and the resultant lesions seemed to us not unlike those of *Lepiospira icterohemorrhagiae* of Weil's disease.

Among the peculiar characters of *L. icteroides* that do not seem to correlate with what we know of the yellow fever infection are, in the first place, the large amount of yellow fever blood necessary to inject into guinea-pigs in order to, sometimes, infect them, (2 to 5 c.c.) when we know that in the same manner, one c.c. of blood taken in the first three days of the disease, regularly produces an infection in man; further, only a minute drop, all that a mosquito needs, in due time will cause numerous cases through its sting, upon non-immunes; by the fact that in Weil's disease, *L. icterohemorrhagiae* is best obtained by injecting a large quantity of the patient's blood into guinea-pigs, even as late as the 8th or 9th day of the disease, while in yellow fever the germ is not present in the blood after the 3rd or 4th day. Another peculiarity is the fact that *L. icteroides* seems to be infective upon the lower animals in every way rather than through the mosquito, when we know by experiment and experience

that yellow fever is not transmissible, in nature, by any other way than through the mosquito. With the leptospira we have at least one instance of natural infection by mouth, of a dog, when neither ticks, fleas, mosquitoes or other insects, many of them present, carried the infection to other puppies in the same litter; the mother obtained the infection through licking her pups, two of which had been experimentally inoculated with *L. icteroides* (5).

If I may be allowed to quote from my own writing, at the International Conference held in Kingston, Jamaica, in the summer of 1924, in a paper that I had the honor to present upon "Yellow Fever Prophylaxis," (6) I said: "the serologic difference between *L. icteroides* and *L. icterohemorrhagiae* are not pronounced; in fact they are no greater than those we find between organisms that form part of a single group, etc."

This question has een refinitely settled by the remarkable work of Sellards and Theiler (7), where they showed that an absolute interrelation exists, the serum of *L. icterohemorrhagiae* causing positive Pfeiffer reaction upon *L. icteroides* and vice versa, the culture of *icteroides* having been furnished by Dr. Noguchi and properly tested before using. Sellards says further (8):

"In our own laboratory Dr. Theiler and myself, (1926) carried out some cross immunity tests in guinea-pigs which were actively immunized against *L. icterohemorrhagiae* and *L. icteroides*. Under the conditions of our experiments we found no differences between the two leptospira."

Other investigators in Africa, (9) (Gray, Connal, Aitken, Smith, 1926) obtained negative Pfeiffer reaction upon *L. icteroides,* using yellow fever convalescent serum.

The same result was obtained, (Sellards) (10) with the yellow fever convalescent serum at Parahyba, Brazil, which serum gave no protection against either *L. icteroides* or *L. icterohemorrhagiae.*

I think that evidence ought to be sufficient to set aside the claimed specific serologic tests of *L. icteroides* with regard to yellow fever.

If my contention is just and correct, and such I believe it honestly to be, what incalculable harm has not been done by appearing to protect against yellow fever by administering a vaccine prepared from an organism that has no connection whatever with the disease! I do not refer to the numerous abscesses produced, as testified to by Dr. H. R. Carter in speaking of the epidemic in Peru, when this method was practiced; no, I have reference to the false sense of security thus imparted to those who believed in the prophylactic virtues of the Noguchi vaccine. Before using it upon the population I think it should have been subjected to the test we applied in Havana to the Caldas-Bellinzaghi serum (11); surely it would have followed upon the same road into oblivion. The same may be said in all respects regarding the so-called curative serum.

But let us see for a moment how *L. icteroides* behaves with regard to the mosquito, the only route that we know by which the yellow fever germ must penetrate and leave the tissues of man.

In my paper read at Kingston, I say (6):

"When a mosquito infected from an inoculated animal, (infected with *L. icteroides*), is, twelve days afterwards, made to bite a non-immune individual causing thereby an undisputed case of yellow fever, then will be time to accept the specific character that is now attributed to Prof. Noguchi's germ. But so long as experiments and tests are restricted to the lower animals, trying to determine there-from the value of the so-called vaccine and sera in yellow fever prophylaxis, *L. icteroides* can have but a laboratory interest."

Noguchi has never reported any experiments with man; I have reason to believe he has undertaken none whatever. It was our intention to try to infect non-immune volunteers with mosquitoes fed on inoculated guinea-pigs, but the culture of *L. icteroides* at our disposal became infected and died before we were ready to attempt the experiments and I have been unable to secure another one for the purpose. If, however, as I believe from the incontrovertible facts presented, *L. icteroides and L. icterohemorrhagiae* are the same, no infection would result, for mosquitoes charged by biting guinea-pigs with their blood teeming with *L. icterohemorrhagiae,* after twelve days cannot reproduce the infection upon either guinea-pigs or man.

Noguchi tries to explain the twelve days extrinsic incubation in the mosquito by alleging that the leptospira requires that length of time in order to multiply sufficiently so that the insect can return it into another individual (12). The facts, however, show that as time passes after the mosquito has sucked leptospira blood, this organism gradually diminishes in number in the stomach and intestines of the insect, proving that the latter is not a proper medium for its multiplication. Such being the case, it is logical to suppose that the longer period that transpires after sucking the infected blood, the less chances there are of its producing an infection, exactly the opposite of what occurs when the mosquito injects the real yellow fever virus.

Recent experiments with *L. icteroides* have demonstrated the correctness of the above surmises, Gay and Sellards (13) have applied mosquitoes, (Aedes aegypti), infected by sucking the blood of guinea-pigs inoculated with *L. icteroides* to non-immune volunteers, obtaining absolutely negative results, after the following manner:

Volunteer A, bit by 36 mosquitoes (Lot 5) 18 days after injection of *L. i.*

Volunteer B, bit by 27 mosquitoes (Lot 5) 25 days after injection of *L. i.*

Volunteer C, bit by 24 mosquitoes (Lot 6) 44 days after injection of *L. i.*

If they had sucked the yellow fever germ instead, any one of those mosquitoes would have produced a case of yellow fever. This was the experiment which I recommended should be undertaken, four years ago.

The serum of those volunteers was not protective to guinea-pigs infected with *L. icteroides.*

The same authors report negative transmission attempts with mosquitoes from infected to healthy guinea-pigs; also, that macerated infected mosquitoes when injected into guinea-pigs soon after their infection will produce the death of the animals, but if some time is allowed to elapse, no infection

of the guinea-pigs could be produced, nor were they protected, because on direct injection of leptospira, they promptly died of the infection (13).

Noguchi ingeniously but very illogically explains why the yellow fever parasite disappears from the peripheral circulation, on the grounds that in a certain culture medium prepared by him, the *L. icteroides* soon leaves the liquid portion and fixes itself upon the semi-solid part. He says (12): "I have often wondered if this peculiar habit of the *L. icteroides* will not explain why they abandon the blood after the first days of the disease rapidly invading the liver and kidneys." He forgets the face that *L. icteroides* multiplies unceasingly and is mostly in evidence in the blood, as time passes after the inoculation of all susceptible animals, regardless of manner of infection.

In conclusion, I may say:

1. That the causative agent of yellow fever has not been demonstrated as yet.

2. That the claims of Dr. H. Noguchi and his disciples for *L. icteroides* as the specific germ of yellow fever have been conclusively disproved:—

(a) Because *L. ictroides* and *L. icterohemorrhagiae* show crossed serologic reactions indicating their identity;

(b) Because yellow fever convalescent serum does not protect against *L. icteroides* while serum from convalescents of Weil's disease does protect both, against *L. icteroides and L. icterohemorrhagiae;*

(c) Because *L. icteroides* gradually increases in numbers in the blood of inoculated animals, while the real yellow fever germ disappears from the circulating blood at the third or fourth day;

(d) Because *L. icteroides* fails to infect mosquitoes so that in due time the latter may infect man;

(e) Because *L. icteroides* is able to penetrate the unbroken skin and produce infection, while yellow fever has been shown to be non-contagious, even through cuts or abrasions of the skin;

3. That any vaccine or serum prepared with the *L. icteroides* can be of no value either protective or curative as regards yellow fever.

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The Treatment of Pernicious Anemia with a Liver Extract*†

By Cyrus C. Sturgis, M.D., Raphael Isaacs, M.D., Millard Smith, M.D.,
Ann Arbor, Michigan

THE discovery by Minot and Murphy (1) (2) that the feeding of one-half pound of mammalian liver daily to patients with uncomplicated pernicious anemia, will cause the red blood count to return to normal limits within six to eight weeks, has received repeated confirmation by numerous investigators. (3) Coincident with the changes in the blood, there is a striking improvement in the patient's general condition and strength. In general, it may be said that all of the symptoms which are directly due to the anemia itself, disappear within approximately two months after the liver treatment is instituted. Having demonstrated that liver contains some constituent which exerts this beneficial effect in pernicious anemia, the most obvious and logical problem which presents itself, is the isolation of the substance to which this property of liver is due. The most essential reasons why this active principle should be isolated are as follows:

1. If a substance can be detected which controls the regeneration of blood in pernicious anemia, this may give additional information bearing on the normal maturation of the red blood cells, which in turn may lead to the discovery of useful information in relation to the more efficient treatment of other types of anemia.

2. From the standpoint of practical therapy the isolation of the concentrated active principle is of great importance. Should the substance prove to be comparatively simple in chemical structure and readily synthesized, an unlimited supply would be assured for the use of patients of limited means who have pernicious anemia. Furthermore, the active principle probably represents such a small fraction of the total liver substance that medication might be simplified to such an extent that the administration of three or four capsules daily would suffice. To maintain the red blood count in pernicious anemia at a normal level, it is necessary for the patients to continue the ingestion of a certain amount of liver or liver extract at regular intervals. The exact quantity which is necessary for the purpose is not definitely known at present. It has been our experience that all patients are unable to consume

*From the Thomas Henry Simpson Memorial Institute for Medical Research, University of Michigan, Ann Arbor, Michigan.

†Presented before the American College of Physicians, March 6, 1928, New Orleans, La.

as much as one-half pound of liver daily for an indefinite period, as some develop an aversion for it which obliges them to discontinue this form of therapy. Such patients do not object to liver in the form of a concentrated extract which can be administered in a half a glass of water or other liquids. An additional advantage of a concentrated extract is that it can be taken between meals and the patients are free, therefore, to consume foods of their own choice at regular meal hours. Moreover, some patients have complained that an adequate supply of calf's liver is not always available and furthermore, under various circumstances, such as traveling, it is not always possible to obtain the necessary amount of liver daily. The preparation of a concentrated and potent liver extract is of the utmost practical importance, therefore, to the successful treatment of the disease.

The method of preparing such an extract was reported by Cohn, Minot and their collaborators in the spring of 1927 (4) and through the courtesy of these investigators and the Harvard Pernicious Anemia Committee,* we were permitted to give this substance an extensive clinical trial before it was released for widespread use. The extract is prepared in a manner similar to the method shown in chart I which involves treating the raw minced liver first with alkali, then acid, in order to remove the liver proteins. The coagulable blood proteins are then removed by heating to 70 degrees C. Additional steps are extracting the remaining solution with ether and then alcohol. The alcohol-ether insoluble residue contains the active principle. The substance thus prepared is a yellowish, granular powder, which represents approximately 1% of the whole liver. It has a slightly disagreeable, characteristic taste and is soluble in water but insoluble in ether and alcohol. According to Minot (5), it is of a non-protein nature and is free of all carbohydrate and lipoids. The earliest reports of its composition stated that traces of iron and sulphur were present but more recent statements (5) indicate that the iron may be removed without effecting the potency of the substance. Minot believes that the beneficial effect produced by this preparation is not due to any known vitamins but suggests that the active constituent is a polypeptid or nitrogenous base (5). West (6) has reported improvement in five consecutive patients with pernicious anemia, all of whom received an alcohol-ether soluble fraction of fresh beef liver. This substance studied by West, therefore, differs from the Minot-Cohn extract in its characteristics as the latter is insoluble in ether and alcohol.

*The extract was prepared by Eli Lilly & Company, Indianapolis, Indiana, under the supervision of this Committee.

THE EFFECT OF LIVER EXTRACT ON THE GENERAL CONDITION OF THE PATIENT.

The effect of this substance when used in the treatment of twenty-eight patients with pernicious anemia forms the basis of this report. The powdered extract made from one pound of raw liver was given once daily, but in a few instances the daily dosage was increased to the equivalent of 1½ pounds. After experimenting with many different vehicles, it was observed

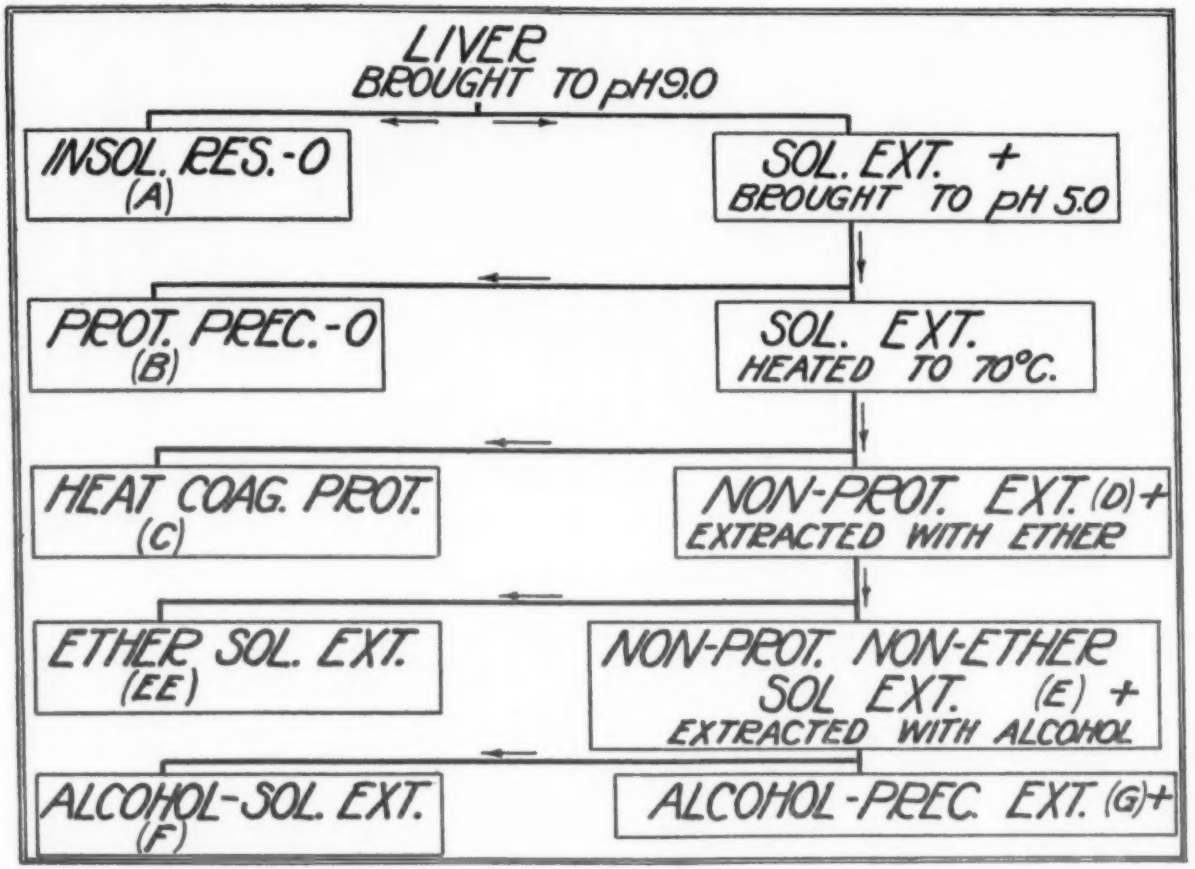

CHART I.—The preparation of liver extract according to the method of Cohn and associates. The capital letters in brackets designate the fraction; + indicates that the fraction contains the active principle, O that it is inactive.

that the slightly disagreeable taste could best be masked by dissolving the powder in tomato juice or tomato bouillon immediately before it was taken by the patient. As much as the equivalent of 1½ pound of liver can be dissolved in one-half glass of water. The effect of the liver extract is entirely similar to that observed following the administration of an equivalent amount of cooked or raw liver. The earliest sign of improvement is usually an increase in the patient's appetite which is noted within three to five days after the treatment is instituted. Coincident with this is a disappearance of nausea, vomiting and other gastro-intestinal complaints. If diarrhoea has been present it usually disappears following a few days of treatment. A few patients, however, who have not had this complaint previously, have developed a mild and transient diarrhoea after liver extract had been given for several days; the same dosage was continued and the condition disappeared without additional treatment. The fever and associated tachycardia which are observed frequently in pernicious anemia during a relapse usually subside rapidly. The patient soon gains strength and all of the symptoms which are directly related to the anemia disappear within six to eight weeks. Unless some complication exists, such as advanced changes in the spinal cord, the patient is able to resume a normal existence.

Tingling sensations in the fingers and toes remain unchanged, although some patients, because of their improved subjective condition, do not notice it as much as when they were sick, while others, being relieved of other symptoms, have their attention directed more fully to it. The change in color of the skin is noteworthy. Frequently on the third or fourth day, and occasionally during the first or second week, the skin of the chin, tip of the nose and later the cheeks begins to flush and appear red, forming an odd contrast to the pale and often icteric appearance of the surrounding areas. Following this the pads of the fingers and later the palmar prominences likewise appear red. As this change is localized and is noted frequently before there is a significant increase in the red blood count, it is probably vasomotor in nature. After the third week, and occasionally earlier, the last sub-icteric traces leave the skin and sclera. With the progress in the improvement of the general condition the stools, which frequently had an extremely foul odor during a relapse, became more normal in odor as well as in general appearance. In those patients in whom the gastric physiology was studied after the onset of the remission, there was no return of free hydrochloric acid in the stomach contents. After the administration of the liver extract, many of the symptoms which had previously been considered as associated with an achlorhydria (belching, feeling of fullness, epigastric distress, anorexia, nausea) were no longer noted. These observations offer material for revision of some of our concepts of the physiology of gastric digestion.

Changes in the blood following the treatment with liver extract and liver.

The effect of treatment with the liver extract on the blood in twenty-eight

patients with pernicious anemia is shown in Table I. It is to be noted that all of the patients before treatment had a low red blood count and in the red cell count had been observed. The effect of the administration of one-half pound of cooked or raw liver to a number of patients for

TABLE I.

Patient	Initial erythrocyte count	Final erythrocyte count after liver extract therapy	Number of days of liver extract therapy	Erythrocyte count after additional days of liver therapy	Number of additional days of liver therapy
	Million cells per cu. mm.	Million cells per cu. mm.		Million cells per cu. mm.	
Ki	.50	3.10	21	5.00	82
Ry	.63	3.80	42		
Ba	.80	3.80	23	5.80	33
Or	.80	4.10	47	4.90	25
Be	1.00	3.80	34		
Ge	1.10	5.20	46	5.40	49
Ov	1.20	3.50	15	5.30	31
Wi	1.20	2.60	24	5.00	51
Cr	1.20	4.70	60		
Hu	1.30	3.10	12	4.80	58
Sm	1.30	3.60	29	4.60	56
McC	1.40	4.00	24	5.10	35
Bau	1.50	2.70	24	4.20	77
Sc	1.50	4.10	24	5.40	25
Ca	1.70	5.00	44		
De	1.80	3.70	26	5.70	91
Jo	1.80	4.50	40	5.70	16
Wr	1.90	3.90	19	5.00	24
Cl	2.00	4.60	14	5.20	44
Zi	2.10	4.00	44	5.60	17
Si	2.20	2.50	7	5.40	86
McK	2.30	3.60	30	4.80	56
Os	2.30	3.30	19	4.50	31
Ro	2.30	5.00	33	5.30	31
Gi	2.30	4.20	21	5.30	29
			26		
Va	3.60	4.50	14		
Mo	3.80	4.60	15		

in each instance there was a very striking increase following the use of liver extract. In a number of patients the use of liver extract was discontinued and the patients given one-half pound of liver daily after a convincing rise a variable period of days is shown, therefore, in addition to the results obtained by the use of the liver extract. From observation of this series of patients it seems reasonable to deduce that in those with uncomplicated pernici-

ous anemia the red cell count can be increased to normal by means of a liver extract, prepared according to the method devised by Cohn and Minot.

As Murphy, Monroe and Fitz (7) have emphasized, the earliest response to the feeding of liver is an increase in the number of reticulocytes of the peripheral blood which is usually apparent a week or more before the rise in the total red blood count can be demonstrated.* This increase is rarely absent in patients who have a low red blood count. It is observed within three to six days after the treatment is begun and usually reaches its height on the seventh or eighth day; following this there is a decrease in the percentage of reticulocytes and by the twenty-first day the number is less than three per cent. After the reticulocyte percentage reaches its maximum and begins to decrease, there is often a second but less marked rise in the percentage before the final diminution starts. In general, it may be said that the maximum height of the reticulocyte increase bears an inverse relationship to the level of the red cell count at the beginning of the treatment as shown by chart II. From the chart it is seen that with an initial red cell count which varies between 0.5 and 2.0 millions per cubic millimeter, the average maximum increase in reticulocytes is approximately 18 per cent; when the initial count is between 2.3 and 2.7 millions per cubic millimeter, the average maximum increase is 8 per cent. when the initial red cell count is between 3.5 and 5.2 millions per cubic millimeter, there may be no significant increase in reticulocytes. This inverse relationship is emphasized further in chart III in which the general curve indicates very clearly that the lower the initial red cell count, the higher is the percentage increase in the reticulocytes. The increase in the percentage of reticulated red blood cells, therefore, is a very constant and reliable criterion of the effectiveness of the liver substance under trial, provided the initial red cell count of the patient is not greater than 3 million per cubic millimeter. Furthermore, when the increase in reticulocytes does occur, it is a very dependable indication that the total red cell count will eventually reach normal with further appropriate treatment, unless some unusual complication arises. Chart IV indicates changes in the peripheral blood of a patient

*The reticulocytes were stained and counted in the following manner: A 0.3 per cent solution of brilliant cresyl blue (National Aniline and Chemical Co.) was made in physiological salt solution and filtered through filter paper. The blood smear was prepared upon a cover glass by placing a drop of blood upon one cover glass, dipping a tooth pick into the brilliant cresyl blue solution and then mixing the blue solution adhering to the toothpick with the drop of blood until the blood assumed a bluish tint. Another coverslip was then placed over the stained glass and when the film had spread out evenly the cover slips were quickly pulled apart by slipping them sideways. To secure even distribution of the cells, the cover slips were thoroughly cleaned, first with soap and water, then distilled water and finally alcohol. Just before using them they were polished by vigorously rubbing over a piece of typewriter paper, placed on a flat table. After the smear was dried, it was stained in the usual manner with Wright's stain. The number of reticulocytes observed during the enumeration of the thousand red blood cells was expressed in per cent of the total number of cells counted.

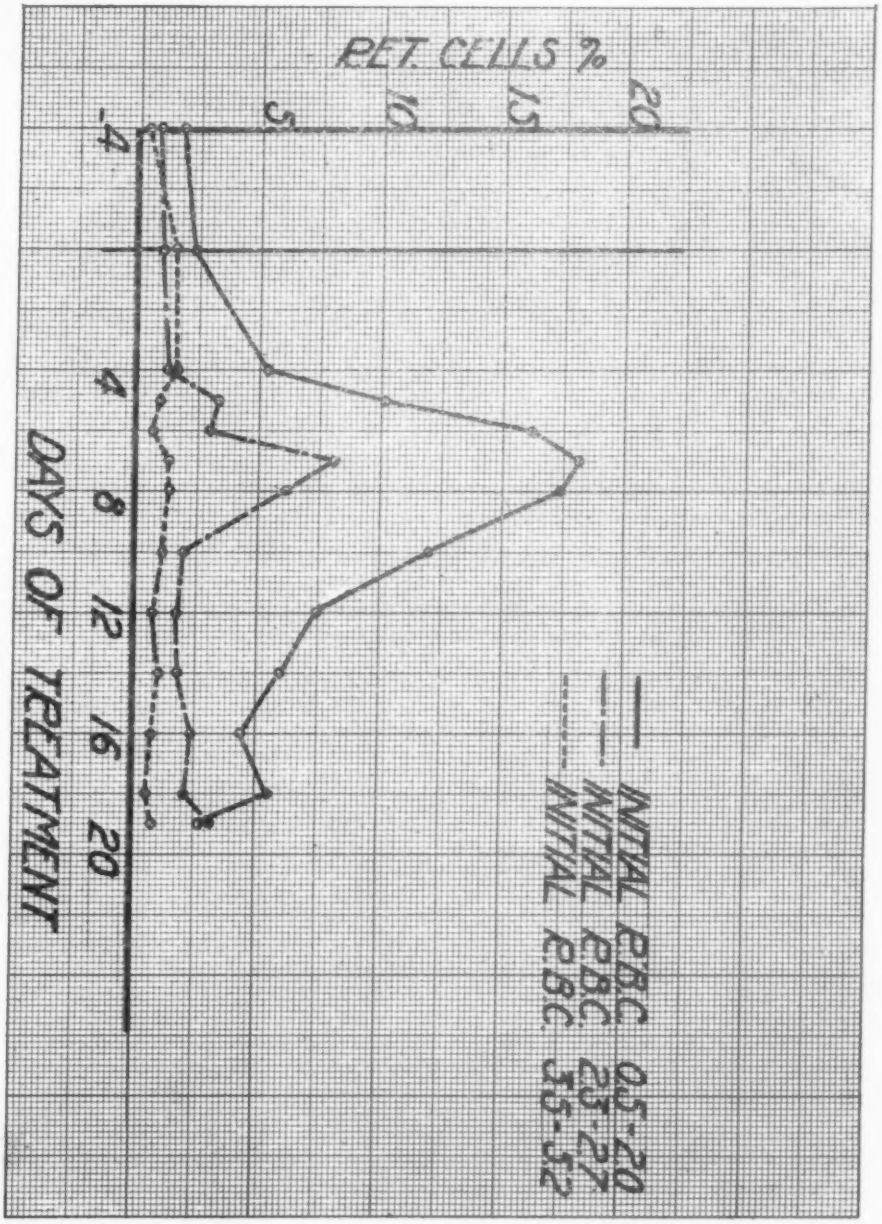

CHART II.—Curves showing the average daily change in the reticulated cell count after instituting liver extract therapy in 18 patients whose initial erythrocyte count ranged between 0.5 and 2.0 million cells per cu. mm., 4 patients with initial erythrocyte counts between 2.3 and 2.7 millions and 2 patients with erythrocyte counts between 3.5 and 5.2 millions.

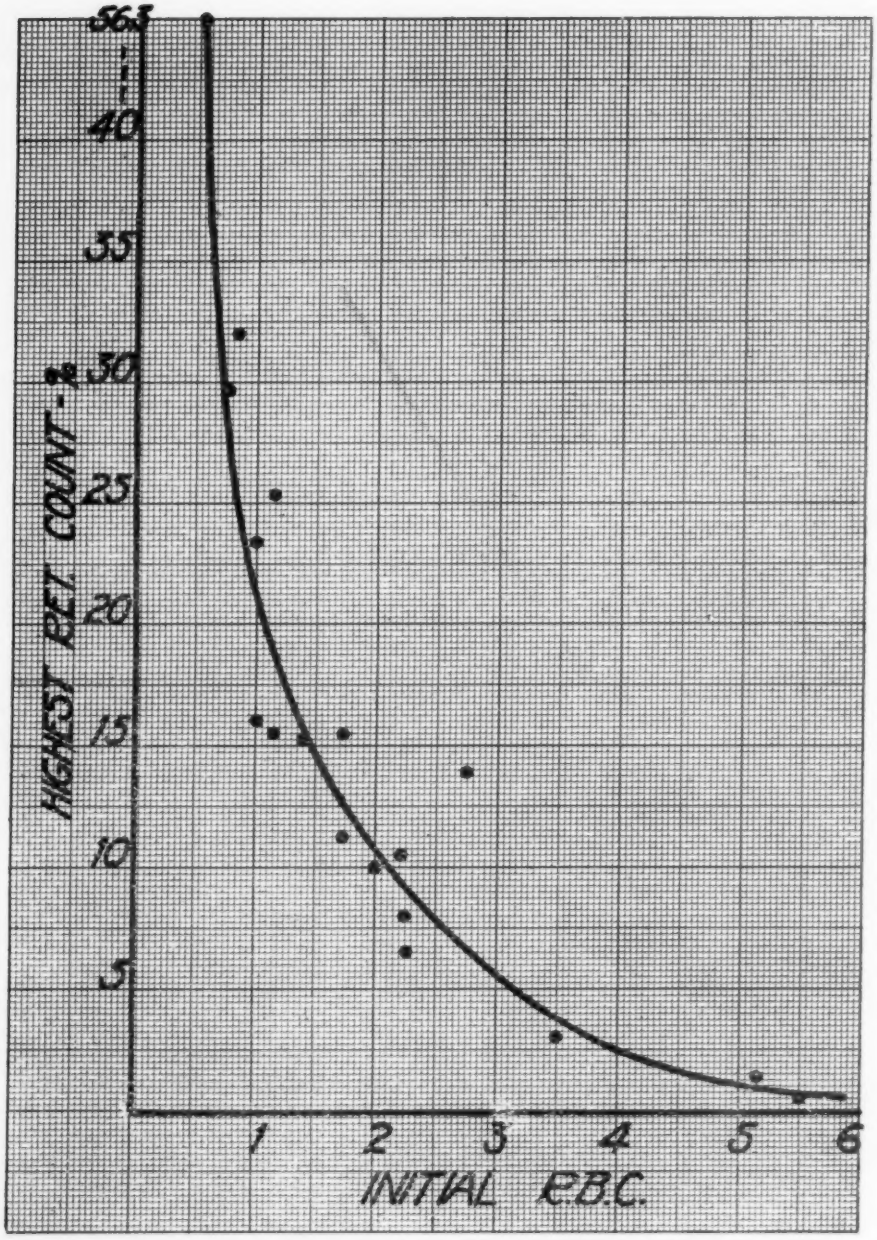

CHART III.—The maximum rise in reticulocytes (per cent) shown by 28 patients whose initial erythrocyte count is indicated by millions per cu. mm. on the abscissae.

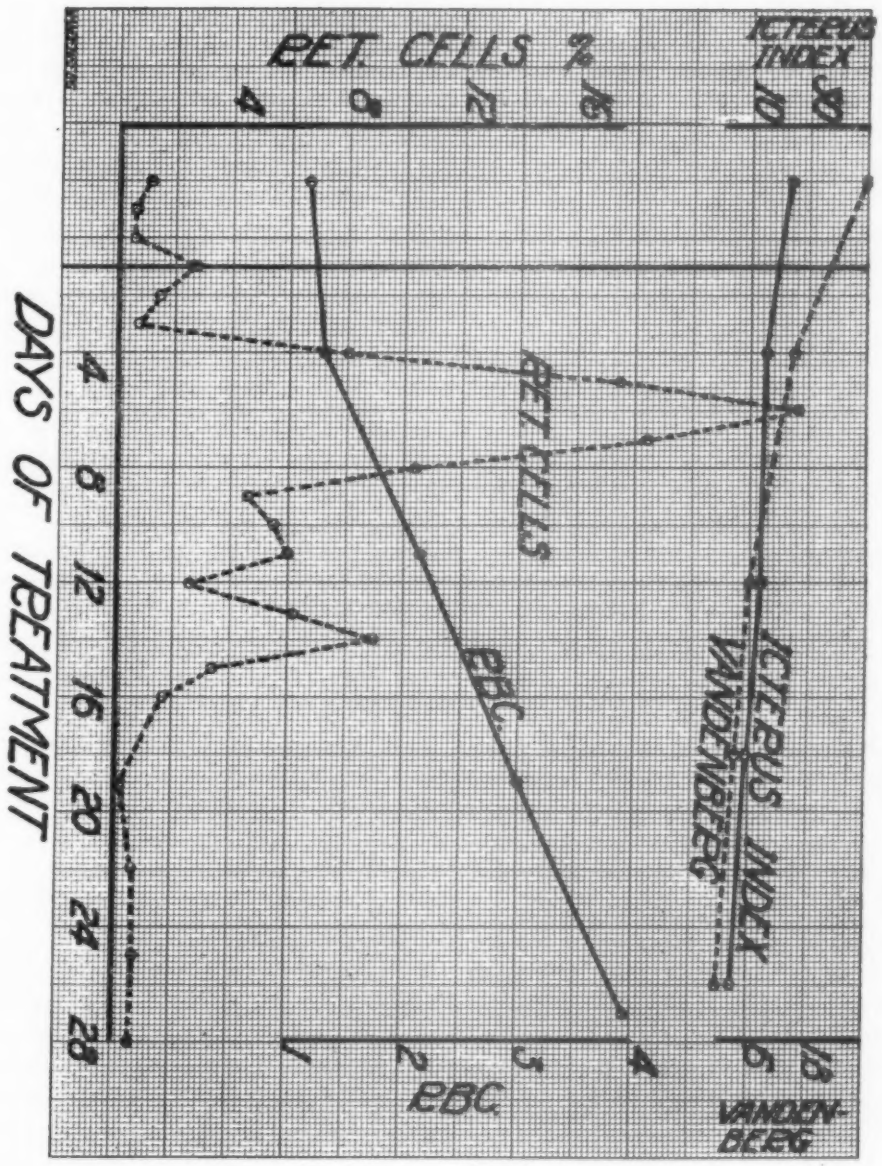

CHART IV.—Daily changes in the blood examination of a representative case of pernicious anemia taking liver extract. R.B.C. = millions of erythrocytes per cu. mm. Ret. cells = per cent reticulocytes. van den Bergh = mgs. bilirubin per 100 c.c. of serum.

with pernicious anemia before and after daily administration of an amount of liver extract which is equivalent to one pound of liver. Patients having an initial erythrocyte count equal to that of this patient may be expected to show changes chronologically and quantitatively similar to those given in this chart, provided there are no unusual complications present.

The greater increase in the percentage of reticulocytes when the red blood count is low than when it is high, appears to be a function of the special pathology of the bone marrow in pernicious anemia. As Peabody (8) and others have shown, the bulk of the erythroblastic tissue in the blood forming areas is in the megaloblastic, macro-normoblastic and normoblastic stage. This, in fact, appears to be the specific hemopoietic lesion—a failure of the erythroblastic cells to mature to the adult state. The "stimulus" given either directly by the liver material or indirectly through the action of the specific agent on other tissues, secretions or in some unknown manner, causes the cells to proceed with their development. A greater number, therefore, reach the reticulocyte stage than previously and this is reflected in the peripheral circulation by an increase in the percentage and absolute number of reticulocytes . The greater the amount of erythroblastic tissue in the nucleated stage, the greater will be the number of reticulocytes produced when the rate of maturation becomes more normal.

The cause of the second rise in the number of reticulocytes after the "peak" had been reached and the number and percentage had started to decrease, offers material for speculation. It was a fairly common phenomenon in the series studied. Whether this may be explained by assuming that the marrow of a different group of bones was affected or whether this is an unexplained but purely physiological response is a matter for future study.

With the increase in the number of red blood cells in the peripheral circulation, anisocytosis and poikilocytosis become less marked. Following the administration of liver extract, it was observed that the mean diameter of the red blood cells returned to normal or less than normal. This same change has been noted by Medearis and Minot (9) in the blood of patients with pernicious anemia after the feeding of whole liver. Poikilocytosis disappears rather slowly, and some abnormally shaped forms persist to a greater or less degree until the blood count is almost normal. It is suggestive that this phenomenon is not entirely a function of the crowded condition of the bone marrow, but rather related to some other feature of abnormal blood formation.

Coincident with the rise in the number of red blood cells after feeding liver extract, the number of white blood corpuscles rapidly increases to normal or the upper limits of normal. The cell morphology also approaches that of the normal blood. A detailed study of this, which is now in progress, will be published elsewhere. There is a tendency for the blood platelets to increase in number, approaching the normal and at times even greater.

It has been observed by a number of investigators (2) (7) that accompanying the rise in the red blood cells as a result of whole liver feeding, there

is a decrease in the excess of bile pigments of the blood plasma. We have noted that all patients with pernicious anemia have an increase in the bilirubin of the plasma during a relapse as indicated by the icterus index and the van den Bergh reaction. After the administration of the liver extract there was a return to normal within a few weeks and with this there was a disappearance of the yellowish tint to the patient's skin. Furthermore, both the van den Bergh reaction and icterus index gave subsequent normal readings in all patients except a few who suffered a relapse from various causes.

Maintenance dosage of liver extract.

It has been our practice, in treating patients with pernicious anemia, to give the liver extract in amounts equivalent to one pound of liver daily until the blood reaches normal. After it has remained at this level for a period of three or four weeks, the dosage has been reduced to the equivalent of one-half pound daily. Further reduction in the dosage is probably possible but the exact amount which is necessary to maintain the blood at a normal level has not yet been determined, and it is entirely possible that this dosage varies with the individual patient. It is not unlikely that as small an amount as the equivalent of one-fourth pound or less daily may be effective. In one patient who was under our observation for a long period, the dosage was reduced to the equivalent of one-half pound of liver a week. This was obviously insufficient as there was first a rather striking diminution in the hemoglobin percentage of the blood which was followed within two weeks by a drop in the red blood count from normal to two million cells per cubic millimeter.

Under ordinary conditions, in the treatment of patients with uncomplicated pernicious anemia, the only other factor in addition to the liver extract which is essential, is an average well-balanced, normal diet. This may usually be left to the patient's own discretion and the keen appetite which is associated with the general improvement. As Minot and Murphy (*2*) have stated, an excess of fat in the diet does not prevent the regeneration of blood in patients with pernicious anemia following the administration of liver extract. This is illustrated by one of our own patients who ingested daily a weighed diet, composed of 40 to 50 gms. protein, 200 to 250 gms. fat and 100 to 230 gms. carbohydrate. At the beginning of the observation period, the red blood count was 1,780,000 per cubic millimeter. The patient received liver extract in an amount equivalent to one pound of liver daily and the diet as outlined above, for fourteen days. At the end of this time the red blood count was 4.64 million per cubic millimeter and there had been a typical increase in the reticulated red blood cells, which showed the initial rise on the fourth day of treatment, reached its peak of 17.8 per cent on the sixth day, and decreased to below 3 per cent on the thirteenth day. In two other patients with pernicious anemia there was a similar satisfactory response following the administration of liver extract during which time the pa-

tient received a diet high in carbohydrate and lacking in fresh fruits, fresh and canned vegetables and red meats.

No attempt has been made to administer the liver extract by other routes than by mouth except in the case of one patient who received the equivalent of one pound for ten days per rectum. In this patient the reticulated cells rose from 1.0 to 5.6 per cent on the sixth day, which indicated an inconclusive or perhaps slightly successful result.

Two patients who had a cystitis when they came under our care failed to show a rise in the reticulocytes or hemoglobin and erythrocytes when given the liver extract. In another patient the hemoglobin decreased 14 per cent and the erythrocytes diminished slightly while taking the liver extract during a severe upper respiratory infection. Before the onset of the infection the patient's erythrocyte count was three million cells per cubic millimeter so that a rise rather than a fall in the number of red blood cells was anticipated. These observations seem to indicate that acute or chronic infections may inhibit blood regeneration in pernicious anemia despite adequate liver or liver extract therapy.

In a series of pernicious anemia patients having signs and symptoms of combined posterior and lateral cord tract degeneration, it has been noted that the administration of liver or liver extract produces no immediate change in the advanced neurological symptoms although blood regeneration seems to follow the usual course. In certain cases with very early signs of cord involvement, we have noted improvement in the neurological symptoms after the institution of treatment with liver extract and physio-therapy procedures which were designed to strengthen the muscles and develop their control. At present we believe that the prognosis in this complication should be guarded but the results of the changes in the nervous system should not be considered as entirely refractory in every case to appropriate treatment.

Summary.

1. A liver extract, prepared according to the method of Cohn, Minot, et al, has been found to produce the same effects on the regeneration of blood in 28 patients with pernicious anemia as previously have been noted to follow the administration of one-half pound of liver daily.

2. The earliest indication of blood regeneration following the use of this extract is a rise in the number of reticulocytes of the peripheral blood. This rise begins between the third and sixth day, reaches a maximum about the eighth day and the percentage returns to approximately normal limits by the end of the 21st day. At about the tenth day the erythrocyte count and the blood hemoglobin begin to increase. As a rule the blood picture has returned to normal by the end of the sixth to eighth week of liver extract therapy.

3. The earliest clinical signs of improvement are increased appetite and sense of well being, often appearing as early as the third day of liver extract therapy and usually by the end of the fifth day.

4. It has been noted in three pa-

tients with active infections that no improvement followed the administration of liver extract as long as the infection persisted.

5. Improvement in the signs and symptoms of combined posterior and lateral sclerosis of the spinal cord did not parallel the regeneration of blood, although slow improvement in the neurological condition has frequently followed the combined use of liver extract and physiotherapy.

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The Evolution of the Modern Treatment of Pulmonary Tuberculosis*

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IN the treatment of disease there is always occurring an ebb and flow in the tide of medical opinion and out of this is finally evolved the accepted standard of practice.

I would ask your attention today to a resume of this evolution insofar as it affects the treatment of Pulmonary Tuberculosis.

Much of the therapeutic teaching of any period is discarded in thirty or forty years as not standing the test of experience or not having a reliable scientific foundation and much of our present day treatment we may be sure will go on the scrap heap in the future; yet, out of a kaleidoscopic array of remedies and measures, there emerges now and again one so well founded and so successful that it becomes a permanent addition to our armamentarium. Thus, step by step, with many backward steps, has evolved the modern treatment of pulmonary tuberculosis. Looking over the ground we see that up to the time of Laennec in the second decade of the last century there was little if anything of the prevailing treatment which we should care to preserve and the foundation for the evolution of which I am speaking can be said to have been laid by his work.

That no intelligent treatment had been developed up to that time is natural enough since there was no thorough knowledge of the pathology of the disease on which to found a reliable diagnosis and a purposeful treatment.

When, however, Laennec, one of the very greatest minds that medicine has ever produced, in the second decade of the last century elucidated its pathology at the autopsy table and, at the bedside, showed the profession by his discovery of auscultation and by building up of the art of physical examination how to make a diagnosis, the eventual development of a rational treatment was assured.

The profession did not have to wait long for the advance to begin. Brilliant minds stimulated by his work were eagerly studying the tuberculosis problem and in the fifties the first fundamental step toward a rational therapy was taken when Hermann Brehmer at Goerbersdorf evolved the Hygienic, Dietetic and Sanatorium treatment which will always be connected with his name. That his method at first had many faults does not detract from the honor we owe him and when developed and corrected by his brilliant pu-

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pil Detweiler at Falkenstein, it became the basis of our modern treatment, and we are too prone to forget the great debt we owe these two pioneers. Thus by the sixties and seventies there began to be a rational and successful treatment carried out in sanatoria in Germany, if not elsewhere, and yielding hitherto unheard-of results. However as is usual in our profession, it was years before the method was generally recognized and applied, largely for lack of Sanatoria, and when in 1895 I was seeking for guidance in building my plan of treatment I had to turn to German authors for light on the method, but there I found it laid down with that beautiful if somewhat meticulous accuracy which is the German gift.

While all this time the knowledge of tuberculosis was increasing enormously, the problem of its etiology was still unsettled and without a knowledge of the cause of a disease its treatment is always handicapped.

True in 1865 Villemin demonstrated its infectiousness but did not discover the organism, but when Pasteur, in the seventies, laid the foundations of bacteriology the time was ripe for the solution of the problem. When a problem is ripe a man usually appears who can solve it and in 1882 the medical world was astonished when a quiet country practitioner, Robert Koch, announced and demonstrated the discovery of the *Bacillus tuberculosis*. The time seemed ready for the solution of the question of treatment along specific lines and, continuing his researches, Koch before long offered the world, which had suffered so cruelly from this scourge for milleniums, a new remedy, Tuberculin, resting on careful reasoning and scientific research and apparently verified by thorough experimental work.

The profession, and indeed the whole world, eagerly grasped at this long awaited specific which was to solve the therapeutic problem and to cure formerly hopeless cases out of hand. It was met by an enthusiasm which it is hard today to realize. Those of us who are old enough can recall the breathless excitement with which the promise of such a remedy was met everywhere. Well do I remember how, as House officer in St. Luke's Hospital, New York, I saw that fine clinician and acute diagnostician Francis P. Kinnicutt almost reverently open the first packet to reach New York from Germany and what hopes filled our hearts. But that was nearly forty years ago and today the question of its value and the indications for its use are still subjects for debate and still unsettled and tuberculin cannot as yet be ranked as a permanent addition to our therapeusis in pulmonary tuberculosis though some men still cling to it. Used at first in dangerously large doses and not fully understood, the early results were anything but encouraging and when the reports from Virchow's autopsy table began to come in with their tales of inflammation of tuberculous tissue and generalization of the process there was a strong reaction from the earlier enthusiasm, which almost stopped its use. However, much careful work, especially by Petruschky, developed a better method of dosage and application which opened a long period, lasting through the first decade of this century, when it was in very

general use. But though all of us who have applied it have recognized its latent possibilities and have seen some brilliant cures, clear indications for its use in pulmonary tuberculosis have not yet been worked out and while, as I said, a few still have confidence in it, the general consensus of feeling among special workers is that, in spite of its value in certain other forms of tuberculosis, in pulmonary tuberculosis, save in a few selected cases, it is a disappointing and at times a dangerous remedy and while it is still being studied and while we all hope that some successful modification of it will be discovered, tuberculin for pulmonary tuberculosis is for the present in eclipse. However, though it cannot, I believe, be as yet recognized as one of the permanent additions to our therapeutics it has served as a splendid stimulus to the scientific study of the tuberculosis problem and has thus been indirectly of immense value. Many sera of which I would mention only those of Marmorek and Maragliano have been strongly advocated as have some vaccines, but none has been able to hold the field or to win a permanent place in the profession's confidence. However, I cannot fail to mention the recent distinguished work of Calmette on B. C. G. for the immunization of infants. Backed up by his great repute as a scientist and an honest man and by a very large series of cases in France and in the Latin countries, it may well be that it will be proven to offer us a solution of the problem of the immunization of infants. But the physicians in other countries have naturally been very cautious in feeding live, even if attenuated, bacilli to babies. At present it can only be called a very promising investigation on a large scale by an able and honest man which calls for futher study.

But while the line of investigation opened up by Koch, which we hoped would carry the evolution of treatment further, has disappointed us, there developed just about the same time in Italy what has proved to be one of the most brilliant advances ever made in phthiseotherapy. I refer to Forlanini's artificial pneumothorax. I say Forlanini's for he unquestionably deserves the credit as the real pioneer and developer of this treatment and his name should always be connected with it just as much as that of a surgeon with a special operation which he has perfected or a physician with a disease whose secrets he has uncovered. First brought out in 1884, the profession, as usual, was slow to give it attention or adopt it though Murphy of Chicago in the early nineties did excellent original work on it. However, it was chiefly brought to public attention and developed in Germany, Sweden and Denmark, and it was not until 1910 that it began to be practiced in this country. But today it is universally recognized as a valuable and reliable procedure and has given us results undreamed-of before in a certain class of severe cases and has become an essential measure in the cure and a permanent addition to our treatment. But there were many cases, where either on account of adhesions, or for other reasons, pneumothorax had failed or had not been applicable, and where the physician, feeling his helplessness, longed to do something more for his apparently hopeless cases. In science even

as in business demand makes supply, and about the end of the last century surgeons, led at first by Tuffier in France and later in Germany by many able workers, among whom Wilms and Sauerbruch stand preëminent, began to develop pulmonary surgery which has most brilliantly met the need of these cases and after much experimental work with various operations and indications we have in Thoracoplastry, Apicolysis, Phrenecotomy, and Phrenicoexairesis well planned measures with a moderate mortality which have added to the list of curable cases a further number of hitherto utterly hopeless patients. These operations form a further permanent addition to our means curing tuberculosis and have made the doctors' task much less difficult and heartrending.

During all these years drugs, which were at first a recognized part of the therapeutics of tuberculosis, have been steadily losing ground save as adjuvants or as symptomatic remedies, when they can be invaluable, and about which the modern doctor knows much too little. However, as cures for pulmonary tuberculosis they are no longer used with the enthusiasm and faith which once marked the profession's attitude to them and no doctor would today claim that he could cure tuberculosis by any drug but rather only that he could benefit the patient by the use of them. Ehrlich's brilliant work on the chemotherapy of syphilis has made the profession hope that some patient experimental chemist will yet discover for us a specific drug, and when Mollgard quite recently made such a claim for Sanocrysin the profession hoped again, but is already disillusionized.

Another remedy which has many centuries or possibly milleniums of an unsystematic use behind it, and which has lately been brought back to popularity by Rollier in Leysin is Heliotherapy. But while certain doctors, some of Rollier's assistants and the workers at Pearysburg and others, use it in cases of pulmonary tuberculosis, Rollier himself told me last year that he did not advocate it in pulmonary cases and most men consider that it is likely to activate sleeping trouble and do harm. However, its results in surgical and glandular tuberculosis such as you see at Leysin are some of the most brilliant that I have ever seen in therapeutics anywhere and it is to be hoped that workers with this means will be able to demonstrate its applicability as a builder of tissue resistance and a fortifier of the constitution, not merely in surgical but in pulmonary tuberculosis. Certainly I have never seen such splendid vitality in tuberculous people as is seen in Rollier's patients. Their skin is almost bursting with health and blood and a comparison of the patients who have been there already some time with their superb appearance of health, their color, their nourishment, their cheerfulness, with the new patients recently come in with their sad, sick faces, their bad nutrition and pallor and their general look of bad resistance, is astonishing and I would give all I have if I felt I could use it in my pulmonary cases as he does in his surgical ones. Whether the sunlight itself or the mere exposure to the fresh cold air or some other factor is the chief thing in the results is not

yet settled. Certainly at Pearysburg, where sun is as often lacking as not, the results are excellent and much more work must be done on this question before it is settled, but there is no fear that so powerful a modality will ever be abandoned. Further, in the quartz light we have an easy means of getting many of the effects of the sunlight indoors if the wind out doors is too strong, while, especially in tuberculous enteritis, it is yielding us results such as we never hoped could be possible, and which have changed our ideas of the prognosis of this terrible disease.

Older probably than any other treatment, Climate has been relied on in pulmonary tuberculosis for endless years. Once unduly vaunted and expected to work miracles, which it often did, the failure to use it with intelligent care justified Osler's wise dictum that "care without climate is better than climate without care" and this abuse of a valuable measure is responsible for its today being unduly disregarded. However, it has too many centuries of good clinical results to its credit to need to apologize for itself; foolishly overpraised and blindly trusted in the past it is paying for this by the underpraise and distrust of many today, but it remains, when wisely chosen and well applied, one of our very best aids in restoring that deficient tissue resistance of the tuberculous patient which is the chief aim of all treatment and after watching its effects for many years in many patients, and, best of all, after actually feeling it in myself, I am sure that self interest is not clouding my judgment when I assert that so valuable a means of restoring the fighting power of the body depleted by the toxins of the tubercle bacillus, will never be abandoned, though we shall doubtless go through recurrent eras of scepticism and over-enthusiasm on the subject. I cannot reject the evidence that I have collected through long years which proves to me that, granted proper conditions, our results in the treatment of pulmonary tuberculosis can be enormously improved and many otherwise hopeless cases saved when they can add properly applied climatic care to their treatment.

There is another method which is essential in the treatment of pulmonary tuberculosis. I refer to Psychotherapy. Although we doctors frequently neglect the psychology of our patients we all of us recognize its importance. The patient is not merely a body to be treated but a mind and soul, to be rebuilt and fortified, and whose condition deeply influences the body; indeed the patient's mentality often dominates the whole case. However, I think this is so well understood by the profession that it is enough to mention it, even though I may return to it later.

Of all the elements in the treatment of tuberculosis which I have thus briefly mentioned there is one which must always take the first place whatever other methods are used in connection with it. I refer of course to the Hygienic and Dietetic treatment and out of this method, so clearly laid down by its founders, and latterly so carefully studied in our sanatoria there has slowly evolved the central idea of Rest as the most important feature in the treatment of this disease. We have, as I have shown you, other invaluable

methods which will never be given up but, whatever their value, rest, at least in the beginning, and often during a large part of the treatment, is the most essential of them all, and though its application may undergo certain modifications it will always be our chief reliance, even if a specific should be discovered. The development of the use of rest dates back to Detweiler's work at Falkenstein and its general adoption has been due to the spread of sanatoria, for they were the laboratories where the hygienic and dietetic treatment could be applied, studied, tested and developed. Here daily clinical experience taught the profession what wonderful cures could at times be wrought in desperate cases by strict bed rest, hence they began to use it more and more, first tentatively, then enthusiastically and today not a few excessively, so that we no longer need to urge its use but rather to warn against its possible abuse. We doctors are prone to go to extremes with every new treatment and it is natural that some have pushed it too far, but while there are many real dangers in the abuse of rest they are not as great as the dangers of the abuse of exercise which was once so common. The case which has been kept at bed rest for years suffers in his morale, in his outlook on life, his ego becomes exaggerated and often his future usefulness is seriously impaired, if not ruined, and he is made into a useless hypochondriac. These are bad things and an indictment of the doctor who allows them, but exercise in a patient with active trouble, with or without temperature, may cause an activation or a dissemination whose results on his health and even life can be disastrous; hence in every case, unless indeed it be the most incipient, there is a time for more or less complete rest. Later there comes a time when exercise must be begun and increased and it takes skill and experience to know when this time is, indeed it takes far more skill to use exercise rightly and wisely than to put a patient to bed and keep him there. Moreover when you put him to bed it takes much knowledge of human nature and psychotherapy to keep his mental attitude sane and healthy. Thus the crux of the situation is the proper use of those two things, rest and exercise, and long ago Brown of Saranac excellently stated the safe rule when he said, "Exercise short of the point of fatigue," and more recently Krause in his booklet "Rest" has put the whole matter excellently in the following words, "Always keeping below the point of fatigue is all there is to this matter of rest in the therapy of tuberculosis; all other methods ever advocated in its treatment will not begin to counterbalance the violation of this single rule of rest and exercise; never become tired, or if tired, rest until completely refreshed."

This is not the place to go into the details of the rest treatment but I would only say that in deciding when to use bed rest and how long to continue it and how absolute to make it, when to graduate the patient to a proper reclining chair, when to begin exercise and how to increase it, we should not, as is too often the tendency, use temperature as our chief guide. Temperature, pulse, cough, expectoration, mental attitude, nervous condition, physical signs and X-ray plates must

all be taken into careful consideration. Some afebrile cases with good symptoms will yet show signs of too much activity in the lungs or shadows of an exudative process on the plates and will need prolonged rest till these show distinct tendency to clear up, however good the patient's apparent condition. Other even slightly febrile patients with physical signs of a slight activity and with shadows of a productive, fibrotic process may safely be gotten up in a recliner and, if under close observation everything goes well, they can be begun on from one to five minutes' walks with safety and with excellent effects on their psyche and general well being. The mental quiet which properly conducted bed rest can give, is often more important than the physical; and high-strung, nervous patients are often better on a porch by themselves with no visitors, whereas most patients do better with porch mates and are benefited by moderate company. We are striving to restore our patients to health, happiness and utility and a normal frame of mind and it takes close study on the doctor's part and that individualization which is often spoken of but not sufficiently used to fit the cure to each patient's needs.

I have very briefly reviewed the evolution of the chief measures used in the treatment of pulmonary tuberculosis since the time of Laennec and more especially during the last forty years, and as I look over the ground I realize that despite the very many remedies that have been advocated from time to time, those that have been sufficiently tried and tested, and have won a permanent place, are few. As I have said, the most important feature of our therapy is the Hygienic and Dietetic treatment, out of which has developed the central feature of our modern practice, Rest. Closely allied to this, as producing local rest, come Artificial Pneumothorax and Pulmonary Surgery, in selected cases. Further, Climate has an assured place as the best restorer of the patient's resisting power. Finally, Psychotherapy, while it too often does not have the attention from physicians which it deserves, is a most important agent which, properly used is powerful for good. Heliotherapy, while invaluable in intestinal and surgical tuberculosis, has not yet won an assured place in pulmonary trouble.

At present then, these are our reliance and, few as they are, the results they yield are remarkable in a large percent of our cases, but there are still too many patients, even among those discovered early, and especially among those who come to us late, who are beyond our power to aid and our treatment must evolve much further if we are to be able to cure them, and I believe that it is towards the development of a remedy based on immunological work to build up the resisting power of the cell that we must labor. Our experience with tuberculin has discouraged us, but in the womb of time lies, I believe, the perfect specific which will some day be discovered and which will make the cell unconquerable by the germ and we must rely upon our research workers, who are now so many, to find it for us.

Meanwhile let us not forget that the measures at present at our disposal,

wisely applied, are daily giving brilliant results.

The longer I treat this disease, the more I realize that these two factors, constitutional resisting power, which we have as yet no scientific means of measuring, but which the physician with experience and judgment can fairly estimate, and moral resisting power which the wise and human doctor well knows how to develop, if it be lacking, are the important factors.

Let the doctor keep this ever before his mind, for as long as he has faith in the possibility of cure he can give hope and fighting power to his patient if the patient is half a man and by such psychotherapy he can accomplish miracles.

Would that some scientific investigator might find the measure of the vital resistance in any case and show us how to develop it. That finally we shall solve this riddle I doubt not. Meanwhile it is in the power of any doctor who takes a live interest in his patient and regards him as a human being and knows how to discover the secrets of his heart, to bring to him aid in his fight such as rest or surgery or climate alone cannot give. Fill our patient's heart with hope and we double the fighting force of every cell in his body. Teach him to smile and we wake up a sunlight in his heart which is the best heliotherapy. Rouse his will power to co-operate with us and our task at once becomes easier. What would the results of our sanatoria be if we could banish the many pitiful and usually concealed anxieties and troubles which are too often gnawing at our patients' hearts and holding them back, and lessening their fighting force.

What discoveries the future may bring to us we cannot know, but while we are far from having attained the control over tuberculosis of which we dream, the results of the modern treatment which I have outlined to you are so good that, granted an early diagnosis and that fundamental resisting power which the majority of our patients have, there is no excuse for pessimism in our attitude save in the minority of cases. The hygienist by his prophylaxis is cutting down its incidence and improving the constitutions of those who may fall its victims. The general diagnostician is infinitely more capable of discovering its early manifestations than the very best man in our profession was thirty years ago, and the therapeutist, having thoroughly mastered the few but powerful measures at his disposal, is returning more and more well trained, dependable patients to a normal, useful life.

Therefore, in closing, my last word is one of hope and of encouragement. Even did we not expect, as we certainly may, any further additions to our knowledge, such as we received from Brehmer and Forlanini, the profession is learning better and better how to fight this plague. Preventive medicine is achieving results hitherto supposed to be unattainable. The constitutions of our people are being raised to a higher level by better conditions of living. Eager research workers are delving into the secrets of nature and I feel very sure that the problem of the cure of tuberculosis will at last be added to the long list of the problems of those other diseases which, in this wonderful century, the intellect of man has solved to the blessing of the race.

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Rheumatic Fever*

By James Craig Small, M.D., *Philadelphia.*

Part I. *Streptococcus cardioarthritides in Rheumatic Fever*

In January, 1927, I described a new species of streptococcus isolated from cultures of the blood and of the pharyngeal exudate in cases of rheumatic fever, under the name *Streptococcus cardioarthritidis.*[1] This streptococcus does not produce any obvious change in the media adjacent to its colony where grown on the surface of agar medium containing blood. It ferments inulin—an unusual property for a streptococcus—and new strains may readily be identified by agglutination with a monovalent immune serum.

This microorganism is found regularly in throat cultures of patients with rheumatic fever or chorea, and we have isolated it in three instances from the blood of patients with rheumatic fever. It is not confined to a limited geographical area. Cultures have been received from England, and others identified in Bierut, Syria.

Inoculated into animals, it produces lesions of the myocardium, pericardium, and cardiac valves; in the joints, their bursae or within the tendon sheaths; and in the central nervous system. These lesions resemble those found in rheumatic fever. They have been observed in rabbits and in horses.

Agglutinins in the patient's blood serum in chorea, and acute rheumatic fever have been demonstrated, the titer is low early in the first attack and rises during convalescence, but declines again soon after recovery.

Opsonins for this streptococcus are low in amount in the patient's serum during the acute stage of the disease. They rise during the favorable course of the disease, regardless of the mode of treatment, and persist at a high level during convalescence and following recovery. In fatal cases low titers have been found.

The action of the anti-serum of *Streptococcus cardioarthritidis* has been observed in 251 patients, 121 of whom were treated in the special rheumatic fever wards of the Philadelphia General Hospital. Prompt beneficial effects follow its use in chorea, and in acute rheumatic fever. These occur with regularity and have been observed in the acute arthritis, the endocarditis, the myocarditis, the pericarditis, the pleuritis, the pneumonitis, and the subcutaneous nodules of rheumatic fever. In chorea, the purposeless twitchings subside promptly and usually disappear within a week after the injection of the serum.

The protection conferred by the anti-serum probably lasts from four to five weeks as judged by the few relapses which occurred early in the

*Read before the American College of Physicians, March 7, 1928, New Orleans, La.

work. This is in accord with the length of the period of passive immunity conferred by other therapeutic anti-sera. To prevent such relapses it is necessary to begin active immunization with the vaccine, soon after the administration of the anti-serum.

Individuals with deep seated rheumatic infections are extremely susceptible to small doses of the vaccine of *Streptococcus cardioarthriditis* injected subcutaneously. They react with exacerbations of the joint symptoms accompanied by febrile reactions, anorexia, loss of weight, abdominal distress, tympanites, nausea, vomiting, precordial pain, cardiac irregularities, muscular twitchings, emotional instability, wakefulness, an increase in leukocytes, and a depression of the opsonic index. Not all of these arise in a particular patient, those appearing depending on the severity of the reaction and on the prominent existing rheumatic lesions. Convalescent cases of acute rheumatic fever have suffered sharp relapses following unduly large doses of this vaccine. These reactions appear to be controlled by the administration of salicylates in adequate dosage. Conversely properly regulated dosage of this vaccine in suitably chosen cases of subacute rheumatic affections renders them free from persistent symptoms. This improvement is attended by an increased tolerance for the vaccine.

Local areas of erythema arise from intradermal injections of the vaccine, or of soluble products of the microorganisms, but these are inconstant and do not furnish a true index of the patient's susceptibility to these products since systemic reactions may arise from an injection which gives no local reaction.

PART II. *The Present Development of the Bilologic Products of Streptococcus Cardioarthritidis and their Application in the Treatment of Rheumatic Fever.*

The anti-serum of *Streptococcus cardioarthritidis* is being prepared both in horses, and in cattle. The bovine and equine anti-sera appear to be equally effective in the treatment of patients. They have been either monovalent or bivalent, being prepared from one or the other, or from both of the two strains first isolated in blood cultures. One of these strains ferments lactose. The other does not—nevertheless their monovalent anti-sera act interchangeably when applied in patients.

Bovine anti-serum has an advantage over equine in that it produces very mild symptoms of serum sickness. It is the exception to have troublesome urticaria following the use of bovine serum, while febrile reactions and arthralgia are rarely observed. It is important to avoid severe serum sickness in the treatment of rheumatic fever, since the arthralgia attending it may be confused with a relapse of the arthritis of the rheumatic fever.

The different lots of anti-serum tested during the course of the development of this product have had to be used in amounts varying from 25 c.c. to 200 c.c. in bringing about comparable clinical responses. The anti-serum (equine) has been concentrated by the globulin precipitation method. This product is required in dosage of from 10 to 20 c.c depending on the

severity of the case. The concentrated bovine anti-serum is in process of preparation.

In the application of the anti-serum in the treatment of the patient, two contingencies must be guarded against. These are hypersensitiveness to the serum of the species employed in its preparation and local reactions of a specific nature arising from the local inflammatory reaction of immunity upon union of antigen and antibody in the diseased tissues. The former may be determined by intradermal skin tests, the latter can be avoided by the broken dose method of administering the anti-serum and by injecting it subcutaneously or intramuscularly. Not more than 5 c.c. of the concentrated anti-serum should be injected as the first treatment. This is followed by another 5 c.c. after 8 to 12 hours and if more is necessary 5 to 10 c.c. may be injected after another 18 to 24 hours.

The vaccine of *Streptococcus cardio-arthritidis* is more difficult to apply clinically, due to the ever present danger of over dosage, and to the appearance of delayed general reactions which may reach their height at from 10 to 14 days after an injection of the vaccine.

To eliminate this secondary reaction the use of the vaccine has been discontinued in favor of soluble products of the micro-organisms. This latter has been designated, soluble antigen. It acts in a manner similar to the vaccine in building active immunity. It is a normal saline extract of the bacteria and is used in two dilutions—a 1:10,000 and a 1:1000 dilution. The initial dose of the 1:10,000 dilution is not greater than 0.1 c.c. subcutaneously. The 1:1000 dilution is reserved for follow-up treatment after a course of the more dilute product, or it may on occasion be used in patients who have recently received adequate amounts of the anti-serum.

The dosage of soluble antigen should be regulated so that an injection will not excite severe local reactions lasting five days or more; so that no febrile reactions occur; so that a persistent acceleration of pulse is avoided; and so that the patient does not lose body weight while under treatment.

Patients with chronic rheumatism are found in the chronic arthritis group and may be identified by the subcutaneous injection of 0.05, or 0.1 c.c. of the 1:1000, soluble antigen. Patients with chronic rheumatism will show marked general and focal symptoms following such an injection. This procedure constitutes a safe diagnostic test.

Tularemia (Francis' Disease)*†

A Clinical and Pathological Study of Forty-Eight Non-Fatal Cases and One Rapidly Fatal Case, with Autopsy, Occurring in Dayton, Ohio.

WALTER M. SIMPSON, M.S., M.D., F.A.C.P., *Dayton, Ohio.*

THE history of tularemia makes fascinating study. It is, in every respect, "the first American disease." The physicians of this country should be thrilled by the thought that not only was this disease discovered by American investigators, but also because its specific etiologic agent, the determination of its modes of transmission from animal to animal and from animal to man, the descriptions of its clinical manifestations and its pathology and bacteriology, were made known by American workers. And leading all, as the guiding spirit which has made this accomplishment possible, is Edward Francis, of the United States Public Health Service. No greater tribute could be paid to the officers of this Service than Vaughan's statement (1) that tularemia is "a disease discovered by the United States Public Health Service." No less than twenty-five contributions, concerned directly with this disease, have appeared in the Public Health Reports.

During the summer of 1907, Martin, an ophthalmic surgeon of Arizona, had observed five human cases of a disease which he attributed to an infection resulting from the skinning and dressing of wild rabbits. In three of these, the primary localization was in the eye. In 1925, Dr. Frederick G. Novy, Professor of Bacteriology at the University of Michigan, found in his files a letter from Martin, dated September 19, 1907. Dr. Novy marked the letter "tularemia" and sent it to Dr. Francis. It stands as the first description of cases of tularemia in the human:

Phoenix, Territory
of Arizona,
September 19, 1907.

Dr. Frederick G. Novy,
Ann Arbor, Michigan.

Dear Doctor:

There have been during the summer several individuals in this locality who have suffered from an infection as a result of skinning and dressing wild rabbits. They were of the so-called "jack" variety. Three of these persons have had their primary lesions in or about the eye. Small abscesses formed in the lids and on the bulbar conjunctiva as well. In one case the cornea was involved, the preauricular gland being involved, as well as the anterior cervical and the submaxillary. At the onset there were chills, profuse sweating and an elevation of temper-

*Presented, in part, before the Annual Clinical Session of the American College of Physicians, New Orleans, March 7, 1928.

†From the Pathological Laboratories of the Miami Valley Hospital, Dayton, Ohio.

ature of from two to five degrees, with rapid pulse, lasting several days. The glands suppurated and all were evacuated. In one case a nodular condition of the lids still remains. There were no deaths; in fact, the illness was not profound. In one instance the infection took place in the foot, and others in the hands, etc., the adjacent lymphatics, of course, being involved.

Yours very truly,
Ancil Martin, M.D.

Francis found anti-*tularense* agglutinins still present in one of Dr. Martin's cases eighteen years after the original infection.

In 1910, Pearse, (2) of Brigham City, Utah, described nine cases of a disease of man which was for several years popularly known as "deer fly fever." To Pearse, then, should go the credit for having first described the *clinical manifestations* of the disease which was called *tularemia* by Francis nine years later. All of Pearse's cases followed horse-fly bites on some exposed part of the body, and all occurred during the month of August. There was one fatality among the cases described by Pearse.

McCoy and Chapin (3), of the Public Health Service, had, in 1911, isolated the specific organism from ground squirrels (*Citellus beecheyi*) dead or dying of a "plague-like" epizootic in Tulare county, California. They gave to the organism the name *Bacterium tularense,* after the county in which their discovery was made.

In 1914, Vail (4), of Cincinnati, described a case of *Bacterium tularense* infection of the eye. In 1915 and in 1917, respectively, Sattler (5) and Lamb (6), likewise of Cincinnati, described cases of "conjunctivitis tularensis." In each instance there was a definite history of the patient having dressed rabbits, and the primary lesion in each instance was on the conjunctiva. In all three of these eye cases, *Bacterium tularense* was isolated by Wherry and Lamb (7). Vail's case, therefore, is the first instance on record in which the disease was diagnosed *bacteriologically.* Wherry and Lamb later (8) isolated *Bacterium tularense* from two wild cottontail rabbits found dead in southern Indiana near the residence of the patient whose disease was described in Sattler's paper.

It was Francis who discovered the unity of the "plague-like disease of rodents" described by McCoy and Chapin and "deer fly fever," the very severe infectious disease of man described by Pearse. In 1919, Francis (9) established a field laboratory at Delta, Utah, in order to investigate the disease then called "deer fly fever." He isolated *Bacterium tularense* from seven human individuals, one of whom had become fatally ill and all having been bitten by the deer fly, *Chrysops discalis,* commonly found on horses. He isolated the same organism from seventeen wild jack rabbits, shot or found dead, and from one ground squirrel. To this new disease of man he gave the descriptive name *tularemia* (10). During this investigation, Francis, as well as Mayne, who worked with him in his field laboratory, acquired the disease. After they had recovered from the severe illness, Francis turned their misfortune to good account by demonstrating in their own blood anti-*tularense* agglutinins.

Francis then demonstrated that the disease could be transmitted among laboratory animals by the deer fly, *Chrysops discalis* (11).

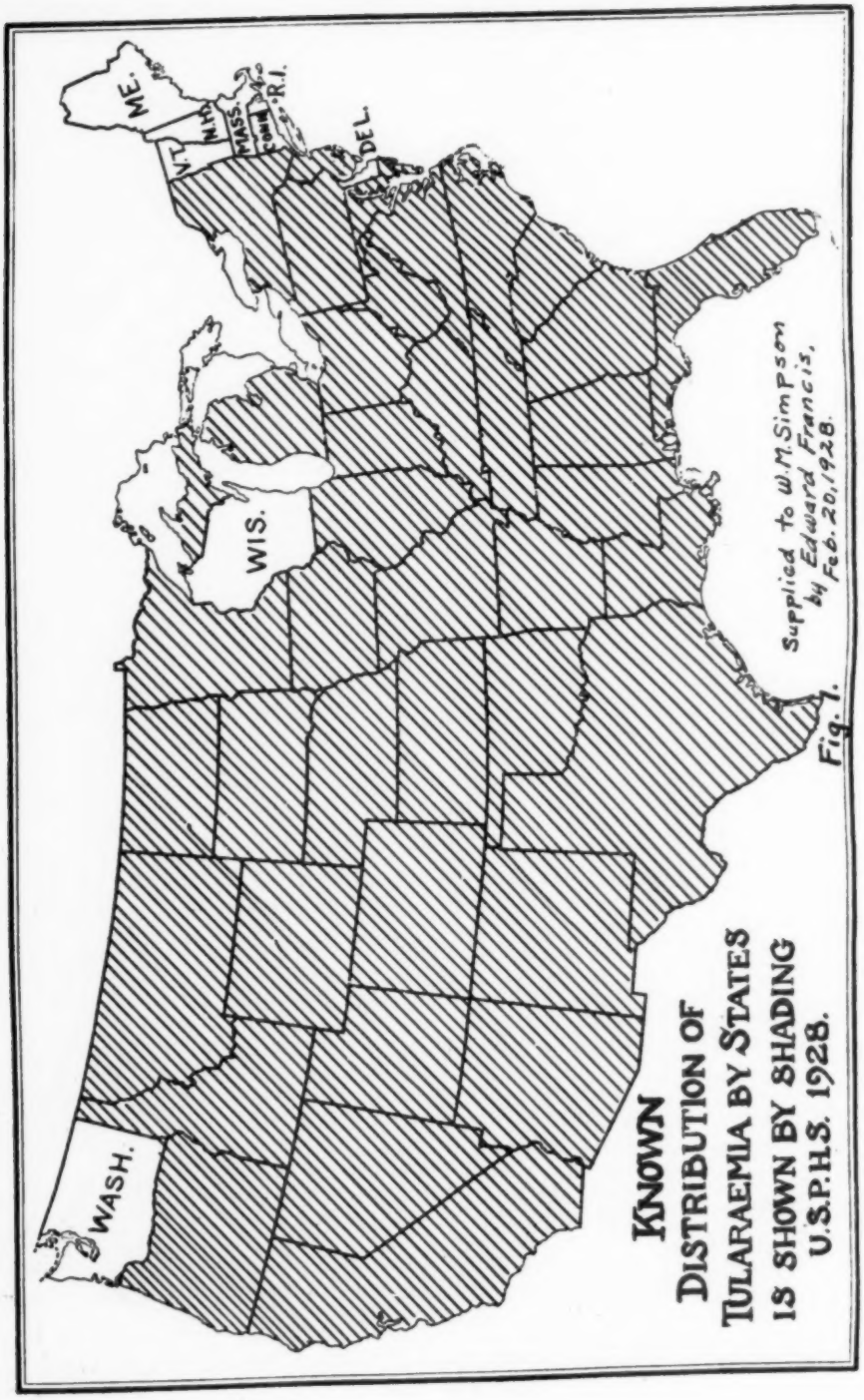
"Rabbit Fever" Among Market Men—Market men have known of this disease, as "rabbit fever," for at least 25 years. The writer has talked with 6 market men who have known of the disease for at least this period of years. One Dayton wholesale poultry dealer has been dealing in rabbits for twenty-one years. In 1908 he acquired tularemia and was told at that time by a wholesaler from St. Louis that he had known of several similar cases in Missouri which had occurred during the 5-year period prior to the onset of the Dayton dealer's illness. After 19 years and 4 months anti-tularense agglutinins still persist in relatively high titre (1:160) in the blood of the Dayton market man. This case, and that reported by Dr. Ancil Martin, constitute the oldest cases on record. The Dayton case is the oldest case in the eastern United States.

Thompson (12), of Washington, D. C., recognized the first case of tularemia in eastern United States, in a market man who had dressed wild rabbits during November and December of 1921. Thompson was told by his patient that he had "rabbit fever" and that "rabbit fever" had long been known among market men. Francis (13) isolated virulent *Bacterium tularense* from 7 of 914 rabbit livers collected in a Washington, D. C. market in January, 1923. He also isolated the organism from the rabbit livers gathered at the same market in December, 1924, and December, 1925. Twenty-two human cases of tularemia have been traced to contact with rabbits sold in this one market.

Identity of Ohara's Disease and Tularemia

Francis and Moore (14) thoroughly investigated a report by Hachiro Ohara: "Concerning an Acute Febrile Disease Transmitted by Wild Rabbits: a Preliminary Report" which appeared in Jikken Iho, a Japanese journal, in March of 1925. After reviewing Ohara's epidemiologic, clinical, bacteriologic, pathologic, and experimental observations, Francis was led to believe that Ohara's disease and tularemia were identical. Between March 12, 1925 and July 10, 1925, four articles describing this disease appeared in Japanese medical journals, but in these no reference was made to tularemia. Two of the Japanese investigators acquired the disease while performing necropsies of infected laboratory animals. Here we have another example of the almost inevitable occurrence of the infection among laboratory workers engaged in investigating this disease. Francis and Moore requested of Ohara sera from the recovered human cases for agglutination tests and fresh human lymph glands for isolation of the organism. These were promptly provided and gave complete serological and bacteriological proof of the identical nature of the disease in Japan, and tularemia.

One interesting incident in the work of Ohara is the transmission of the disease to a human volunteer. Ohara's wife cheerfully volunteered to be inoculated in order to help prove the scientific convictions of her husband. The


ME.
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KNOWN
DISTRIBUTION OF
TULARAEMIA BY STATES
IS SHOWN BY SHADING
U.S.P.H.S. 1928.
Supplied to W.M. Simpson
by Edward Francis,
Feb. 20, 1928.

Fig. 1.

heart's blood and tissue-fluid of a rabbit which had been found dead in a district where numerous human cases of this disease had developed, were lightly rubbed into the back of Madame Ohara's left hand, on January 20, 1925. Twenty minutes later, the adherent material was washed off with soap and water. Two days later, Madame Ohara complained of a mild headache and tenderness in the left axilla. On January 24, the temperature rose to 37.4°C. and she complained of general malaise; one of the left axillary lymphnodes became enlarged to the size of a soy bean and the patient was confined to bed. The next day she complained of chilliness, articular pains, headache, a general feeling of languor, constipation, and numbness of the extremities. On the next day an axillary lymphnode reached the size of the end of the index finger and became very tender, and the inguinal glands became swollen and slightly tender. The fever reached its maximum of 39.8°C. on January 26. On February 7, two axillary nodes the size of a pigeon's egg, and several smaller glands were removed at operation; the two large glands had suppurated. Histologic examination of these glands showed round cell infiltration, dilatation of the blood vessels, extravasation of blood, small abscesses, caseation and giant cells. Eight months after the onset of this illness, Francis found that the serum of Madame Ohara agglutinated *Bacterium tularense*.

Mode of Transmission

In 1924, Parker and Spencer, (15) of the United States Public Health Service, while engaged in investigations on Rocky Mountain spotted fever in the Bitterroot Valley of Montana, recognized that the common wood tick of that region, *Dermacentor andersoni*, was a host and transmitter of tularemia. They had been led to suspect that this tick was a "carrier" of the disease two years before this, when they found typical gross lesions of tularemia in guinea pigs into which ticks had been injected as a routine test for the presence of the virus of Rocky Mountain spotted fever. In May, 1923, they isolated *Bacterium tularense* from guinea pigs inoculated with adult wood ticks collected from the vegetation in the Bitterroot valley. They likewise found the infective agent to be present in ticks collected from horses, mountain goats, wood chucks, mountain rats and Columbian ground squirrels. They transmitted the infection to rodents by the wood tick, *Dermacentor andersoni*, and by the rabbit tick, *Haemaphysalis leporis-palustris*. Furthermore, they (16) demonstrated hereditary transmission of the infection by female ticks (*Dermacentor andersoni*) through their eggs from generation to generation. They found that tularemia existed in the snowshoe rabbit and jack rabbit of Montana. They (17) showed that 7 of the species of Montana rodents, and the coyote (*Canis lestes*) (18), were susceptible to tularemia. Finally, they (19) demonstrated the presence of anti-*tularense* agglutinins in their own blood and in the blood of four other workers in their laboratory. All six of these laboratorians had acquired the disease while engaged in this work and in three instances the direct cause was infected ticks.

In the number of cases of tularemia reported, Montana ranks second in the states of the Union — fifty-nine confirmed cases. Of this number, 13 are known to be directly due to tick bites and in 10 other instances a tick bite or contamination by tick tissues or excreta was the probable cause. These ticks constitute a permanent reservoir of infection. The infective agent, widely distributed throughout their bodies, has been demonstrated in the lumen of the gut, in the cells of the gut wall, in the Malpighian tubules, in their circulatory fluid, and in their feces. They harbor the infection throughout their lives and carry it over from winter to winter. They constitute ideal transmitters of the infection. Fortunately, these ticks are found in a restricted area in this country—principally in Montana and the nearby states. Likewise the transmission of tularemia to man through the agency of the horse fly, *Chrysops discalis*, occurs in the Northwest, principally in Utah and the surrounding states. Neither the tick nor the horse fly play an important part in the transmission of the disease east of the Mississippi, although a tick (species undetermined) has caused a few cases in Louisiana and Tennessee.

The vast majority of cases of tularemia have been caused by contamination or self inoculation. It is this method of transmission which has obtained in practically every case east of the Mississippi river. Including the cases presented in the present paper, Ohio has reported 75 proved cases of tularemia—more than any other state. Most of the cases have occurred in market men, who have skinned and dressed wild rabbits; in housewives or servants who have dressed rabbits for the table; in hunters who have dressed rabbits during the hunt; in farmers or ranchers who have picked infected ticks or flies from their horses or cattle, or who have cut up jack rabbits for fish bait, coyote bait or for feed for domestic animals. The score of cases which have occurred among laboratory workers have resulted from handling infected laboratory animals or infected ticks. Every case in the series reported in this paper occurred as a result of self-inoculation.

There is no evidence at hand which would indicate that the disease has been acquired by eating rabbits infected with tularemia. There is some experimental evidence, however, which would lead one to the conclusion that insufficiently cooked rabbit meat might be dangerous as food. Freese, Lake, and Francis (20) took an experimental rabbit dead of tularemia, rolled the pieces usually prepared for the table in graham flour and fried them in grease over a hot gas flame for ten minutes. At the end of this time a brown crust had developed and the meat gave the appearance of being sufficiently cooked. The pieces were then carved, the successive layers of muscles appearing white and well cooked until near the bone some red streaks of insufficiently cooked muscle surrounded by red juice were seen. The red muscle was injected into two guinea pigs and the red juice was injected into four guinea pigs, all of which died acutely with the characteristic lesions of tularemia. *Bacterium tularense* is relatively thermolabile. It succumbs in

10 minutes in cultures and in splenic tissue when heated to 56° to 58°C.

No disease has ever claimed so many victims among laboratory workers as has tularemia. Fifteen cases have occurred among laboratorians of the United States Public Health Service. Two cases occurred among the Japanese investigators. Three cases occurred among laboratory workers in the Lister Institute of Preventive Medicine, London, England, after they had autopsied animals infected with cultures of *Bacterium tularense* which had been sent to the Institute by Francis, for inclusion in their National Collection of Type Cultures (21). To quote from the report of the Great Britain Medical Research Council, 1921-1922: "It was deemed inadvisable to continue the propagation of this dangerous organism in the National Collection." Most of these laboratory cases occurred in physicians who were thoroughly trained in the handling of virulent bacterial cultures. The portal of entry of the organism in these cases is still a matter of conjecture, since most were of the typhoid type, with neither primary lesion nor bubo.

Prior to 1924 but 15 cases of tularemia had been reported. With the exception of the 12 Japanese cases and the three cases occurring in English laboratorians, none has been reported outside of the boundaries of the United States. Cases have now been reported in every state in the Union, except the New England States, Delaware, Wisconsin and Washington. Up to May 1, 1928, reports of 613 authentic cases have come to the attention of Francis (22). This fact has but one significance, namely, that tularemia is an exceedingly common disease and the physicians of this country have acquired the ability to recognize it.

There is no record of any transmission of the disease from man to man except in the case reported by Harris (23) in which a mother is thought to have acquired the disease as a result of pricking her thumb while dressing the tularemic ulcer of her son, who had been bitten by an infected deer fly.

The disease is unquestionably transmitted from rabbit to rabbit in nature through the agency of blood sucking lice, flies and ticks. In this way the disease is perpetuated. There is no record of the disease having been found in domestic rabbits raised in rabbitries, although such rabbits are very susceptible to experimental inoculation.

Clinical Manifestations

Tularemia shows remarkable seasonal variation east and west of the Mississippi River. In the western states the onset of human cases corresponds to the season of the greatest activity of the wood ticks and deer flys. *Dermacentor andersoni*, the tick most often responsible, as intermediate host, for the dissemination of the disease in certain states shows its greatest activity during March, April, May, June, July and August, while the deer fly, *Chrysops discalis*, is at the season of its greatest activity from June to September. Furthermore, the jack rabbits are found almost exclusively west of the Mississippi river and no laws prohibit their destruction. Human cases caused by cutting up jack rabbits occur during the months from April to October. East of the Mississippi the situation

is entirely different. Here the incidence of the disease conforms to those months during which the state game laws permit the hunting of wild cottontail rabbits, namely, November, December, and January. Every individual included in the Dayton series acquired the infection during November. This fact has considerable diagnostic importance.

As the result of the analysis of over 500 case reports, four distinct clinical types have been recognized:

1. *Ulceroglandular,* the most common type, in which the primary lesion is a papule which develops at the point of inoculation, usually the finger or hand in cases acquired by direct contact. The papule rapidly becomes painful and swollen and suppurates in the center, liberating a necrotic core and leaving an ulcer about three-eighths of an inch in diameter, with reddish elevated periphery, a necrotic base, and a sharply punched-out border. These patients usually complain, within a day after the onset of the illness, of tenderness or pain in the regional lymphnodes draining the site of inoculation. On examination these glands will be found to be tender and enlarged. Only in rare instances are glands other than the regional glands involved. It is a peculiar circumstance that the glandular pain frequently precedes by about 24 hours any definite reference by the patient to any pain or swelling at the site of inoculation. The ulcer heals very slowly and healing is apt to be delayed if the primary lesion is incised. In every one of our cases in which surgical incision was done the patients invariably felt worse after the incision. There is abundant clinical evidence to indicate that one should not interfere surgically with the primary lesion. Incision is usually fruitless because the lesion is essentially a granuloma and there is little or no pus.

In the majority of our cases, inoculation occurred as the result of a perforating wound produced by a sharp fragment of rabbit bone. The hands of market men who have dressed rabbits usually show multiple lacerations produced by the sharp edges of broken ribs and long bones.

The skin overlying the enlarged and painful regional lymphnodes becomes reddened and in about one-half of the cases the skin becomes thinned and the glands drain spontaneously. In the remaining half of the cases the abscess does not burrow its way through the skin but the glands remain hard and rather tender for two to five months and ordinarily return slowly to normal size. In several of our old cases, firm enlarged axillary and epitrochlear nodes persisted for many years. In 27 of our cases the axillary mass became fluctuant and surgical drainage was instituted with good results. The patients invariably felt much better after the surgical drainage of the suppurating axillary glands. In 4 of our cases glands other than the regional glands were involved. It is rather difficult to determine whether or not the enlarged nodes in the axilla of the side opposite to the primary lesion were not the result of an infection in the other hand with no visible primary lesion.

Sporotrichosis-like nodular lymphangitis over the forearm and arm has been described in 33 previously re-

ported cases and occurred in 6 instances in our series. In our cases and in most of those described in the literature these nodules were at first firm and freely movable but later suppurated.

The period of incubation varies from one to five days. In the majority the onset occurred on the second, third or fourth day after inoculation. The onset is sudden and may occur while the patient is asleep or while he is in the midst of his work, and is characterized by "grippe-like" symptoms; severe headache, fever, chills and sweats, aching pains in the back and extremities, vomiting and marked prostration. Many patients are delirious from two to five days.

2. *Oculoglandular type.* These cases differ from those described above in that the primary localization is in the conjunctival sac instead of in the skin. Of 22 cases collected by Francis, 19 had unilateral involvement of an eye and regional glands, while three had simultaneous bilateral involvement of both eyes and the regional nodes on both sides, together with enlargement of the upper cervical lymphnodes. The early manifestations are excessive lachrymation, marked irritation, edema of the lids and surrounding tissues, edema of the ocular conjunctiva and usually a papule on the inferior palpebral conjunctiva. At the same time there occurs enlargement and pain in one or more of the following groups of lymphnodes: preauricular, parotid, postauricular, submaxillary, anterior cervical, and in a few severe cases the axillary group. The same severe constitutional symptoms are present as in the ulceroglandular type. In many ways, the diseases long known to ophthalmologists as Parinaud's conjunctivitis and *conjunctivitis necroticans infestiosa* (24) are clinically similar to *conjunctivitis tularensis.* Parinaud's original descriptions reads exactly like the present-day descriptions of tularemic conjunctivitis. Parinaud originally ascribed the disease to "a contagium derived from animals" and recent ophthalmological text books state that the etiologic agent is not known (25).

3. *Glandular type.* In this type there is no visible primary lesion. In 9 of our cases the most careful scrutiny of the fingers and hands revealed no grossly visible papule or ulcer. In all other respects the disease simulates the ulceroglandular type. There is abundant clinical and experimental evidence to show that the organism does pass through unbroken skin.

4. *Typhoid type.* In this type there is no primary lesion and no regional adenopathy. Fever is the outstanding symptom. It closely simulates typhoid fever. Most of the cases occurring among laboratory workers fall into this group.

A skin eruption occurs occasionally and may appear anywhere on the body (26). In one of our cases (J. S.) a maculopapular eruption appeared over the upper extremities and neck, while in another (P. S. J.), a maculopapular eruption appeared over the abdomen, thighs and scrotum. In reviewing the literature, the writer was struck by the number of fatal cases which were preceded by a pustular eruption. It would appear as though the develop-

ment of a pustular eruption carries with it grave prognostic significance.

Most cases are characterized by a considerable degree of chronicity. The convalescence simulates that following severe influenzal infections. Three of the Dayton patients worked during their entire illness but in each instance only because they felt forced to do so because of economic demands. Most of the patients were strictly confined to bed for ten days to three weeks. Usually the patient is so weak during the second month that he is unable to exert himself. Many have gone to work during the third month and have been forced to quit and rest for another month or two. Many of our patients have stated that they do not regain their strength for over one year.

The recorded deaths number 23 (3.7 per cent.). Unquestionably many deaths have not been reported. In addition to the one death reported herewith the writer has learned of at least seven others that have occurred during the last ten years in Dayton, which were probably due to this disease. In November, 1926, two brothers, both butchers, were taken violently ill after having dressed rabbits for several days. One brother died three weeks after the onset of his illness; the other recovered after a stormy and prolonged convalescence. Serum of the surviving brother, taken 14 months after the onset of his illness, agglutinated *Bacterium tularense* in relatively high titre (1:320). During Thanksgiving week, 1923, three women dressed rabbits at the C. market, in Dayton. All three became severely ill with "grippe-like" symptoms, together with axillary and epitrochlear adenitis. One of the women (Mrs. C. H.) died in two weeks. Sera of the two surviving women (Mrs. M. H., case XLI, and Mrs. W. H., case XLII) were found by Dr. Francis to agglutinate *Bacterium tularense* in all dilutions to 1:80.

Persistence of agglutinins: Agglutinins are constantly present at sometime during the second week of the illness. An abrupt rise in the titre occurs during the third week, which reaches its maximum (1:1280 to 1:2560) in the fourth to the seventh week. During the eighth week there is usually a slight fall in titre with a gradual decline until, at the end of the first year, the average titre in one series was 1:136. There is at hand sufficient evidence to permit one to conclude that the agglutinins never entirely disappear. In one of our cases (M. T.), agglutinins were present (1:160) after 19 years and 4 months, in another instance (J. H. A.) after 15 years and 3 months (1:80), in one instance (J. C.) after 14 years and 4 months (1:320), in two other instances (R. T. and B. F.) after 11 years and 3 months (both 1:320). The final agglutinating level to which all cases seem to come is about 1:40. Questioning individuals might ask whether the annual exposure to infection while dressing rabbits might not have contributed to the persistence of of the agglutinins. The evidence is against such a view because there are instances of the same persistence in laboratory workers who have not been exposed to the infection in the succeeding years after their original attack. In none of our cases of long duration mentioned above has there been any attack simulating tularemia since the

original attack, even though ten of these men have handled thousands of rabbits since that time. Several Dayton market men have stoutly declared that they have not handled rabbits since they acquired tularemia, and there is no essential difference between the agglutination titre in these individuals and that of those who have continued to handle diseased rabbits. In one laboratorian (E. F.) who has autopsied animals infected with tularemia continually since the original attack in 1919, no rise in titre has ever been noted. Moreover, in a rabbit which has been injected with a culture of *Bacterium tularense* the height of the titre is reached about the 14th day, when the decline begins. Subsequent injections with cultures will not reverse the declining trend of that titre (27). The experience of all investigators is in accord, namely, that one attack of tularemia confers permanent immunity, that agglutinins have never entirely disappeared from any case, and that subsequent exposure to infection does not tend to elevate a *tularense* titre acquired by the original attack.

Diagnosis

It has been aptly said that no one can make a diagnosis of a given disease unless he has that disease in mind. The fact that all but 15 of the 613 cases which have been reported to date have been recognized during the past three years indicates that the physicians of this country have learned to recognize this disease, thanks to the writings of Francis. The onset symptoms closely simulate those of influenza and many of our cases were primarily thus diagnosed. The next most common error has been to consider that the disease was due to streptococcus infection. A few cases simulate typhoid fever. Because of the nodular lymphangitis which has developed in some cases the diagnosis of sporotrichosis has been made. Due to the fact that the agglutinins present in the serum in tularemia will occasionally cross-agglutinate *Bacterium melitense* and *Bacterium abortum*, serologists have confused the disease with undulant (Malta) fever. It would seem that *Bacterium tularense*, *Bacterium melitense* and *Bacterium abortum* show a serologic relationship, in the same manner that *Bacillus typhosus*, *Bacillus paratyphosus A* and *Bacillus paratyphosus B* are closely related sereologically. The proportionately higher titre reached by tularemia agglutinins leaves little doubt as to the diagnosis. On the other hand, pathologists have clung tenaciously to the histopathological diagnosis of tuberculosis because of the remarkable similarity in the granulomatous lesions.

The history gives the most important clue to the diagnosis. The patient usually tells, particularly if questioned about it, of having handled wild rabbits or having been bitten by a tick or horse-fly. The primary lesion first exists as a reddish papule followed by a persistent ulcer, or as a primary conjunctivitis, usually followed by conjunctival ulcers. Almost simultaneously with the appearance of the primary lesion the persistent satellite bubo developes, and these local manifestations are accompanied by chills and fever, sweats, headache, aching sensations in the back and extremities and a feeling of great prostration.

Once the clinical diagnosis has been made it is an easy matter to confirm it. The simplest and best method is to collect 4 to 5 cubic centimeters of the patient's blood, exactly as one collects it for the Wassermann test. Either the serum or the whole blood may be sent to any laboratory which has on hand the necessary *Bacterium tularense* antigen for agglutination reactions. The specimen may be sent directly to the Hygienic Laboratory of the United States Public Health Service at Washington, or to the state health laboratory, if it possesses the antigen. Many state health laboratories are now equipped to carry out this simple procedure. A second method is the isolation of *Bacterium tularense* from guinea pigs inoculated with the blood of the patient or with material taken as early as the first week from the primary lesion or from the enlarged lymphnodes. Francis has repeatedly stated in his publications that all attempts to recover the organism directly from human tissues on artificial culture media have been futile. All investigators concerned with the bacteriological aspects of this disease have emphatically stated that they have been unable to recover the organism by the direct inoculation of culture media with human material derived from the primary lesion or from the regional lymphnodes. The writer succeeded in two instances (J. S. and H. C.) in growing the organism directly upon culture media from the material taken from the walls of the axillary abscesses. The organism thus recovered was passed through three series of guinea pigs. All died within a week with the characteristic gross and microscopic tissue changes and the organism was recovered from the animal's blood and tissues and again inoculated into other animals with similar results. Furthermore, the organisms agglutinated promptly in dilutions up to 1:1280 when tested with known sera. The best growth was obtained upon cystine-glucose-peptone-meat infusion agar (Francis' medium) to which 5 per cent human serum had been added.

Cover glass preparations made directly from the pus evacuated at the time of surgical drainage are of no use in determining the identity of the organism.

Bacterium tularense is a small, nonmotile, Gram-negative organism, which exhibits marked pleomorphism in its growth on special culture media. It appears as a short rod and as a coccus. In a single transfer it may change from coccoid form to rod form, and in many of our cultures rods and cocci, together with transition forms, were present to the smears stained with aniline gentian violet.

Treatment

There is, as yet, no specific treatment. The treatment is entirely symptomatic. Strict confinement to bed is the most important part of the treatment. It is unwise to incise the primary lesion and it is unwise to excise, or even incise, the enlarged glands until definite suppuration is present. The most important phase of the treatment is prophylaxis, and this is best accomplished by education of market men and the laity in general as to the

dangers of the infection and the manner in which it is acquired, by urging thorough cooking to destroy the infective agent, and by the warning that all individuals who handle wild rabbits should wear rubber gloves.

In view of the fact that the agglutinins are retained permanently it seems quite logical to believe that the disease might be arrested in the acute stages by the use of immune serum, particularly that taken from individuals who have agglutinated *Bacterium tularense* in high titre. Because of the fact that we did not know of any old cases when we undertook the present work we were unable to try this procedure this year, but we will be on the sharp lookout for acute cases during the next rabbit season and we will give this method of treatment a thorough trial.

The Dayton Experience

Fatal Case

On the afternoon of the 25th of November, 1927, Mr. F. W., a 25-year-old colored dresser of rabbits and chickens at the J. O. F. market, of Dayton, Ohio, was admitted to the receiving ward of the Miami Valley Hospital as an emergency case. At this time he appeared as a well developed, muscular colored man, appearing to be about the stated age, acutely ill, delirious, and quite unable to give a clear account of his illness. The history was obtained from his wife.

After the onset of the present rabbit season, which, in Ohio, begins on November 15th, the patient dressed several hundred rabbits and chickens at the J. O. F. market. He developed multiple small blisters on his right hand, more marked on the dorsum. His wife attributed these to the immersion of his hands in hot water while picking the feathers from chickens. He continued his work and felt perfectly well until one week after he first noticed these blisters. On the morning of the 22nd of November, the patient arose at the usual time, but complained bitterly of headache. However, he went to work, but about 9 o'clock in the morning he felt considerably worse and was forced to go home and take to his bed. On this day it was noticed that the glands at the right elbow and in the right armpit were swollen and tender. He remained in bed and continued to grow worse. On the morning of the 25th of November he had slight bloody expectoration. He was unable to take food; he vomited for the first time on this morning and became delirious.

In the hospital the patient was exceedingly restless, complained bitterly of pain in his head, in his back and legs, and was unable to move himself. His admission temperature was 106°F. The physical examination, except for the external findings, was essentially negative. The skin over the entire right hand from the finger tips to the wrist showed extensive exfoliation with many deep irregular fissures extending into the corium. There was no well defined ulcer. The skin of the fingers of the left hand showed a much less marked desquamation. The right epitrochlear lymph glands were moderately enlarged, the average size being that of a kidney bean. These were tender to palpation. The right axillary nodes were enlarged to the size of a small orange. These were exquisitely

painful and caused the patient to cry out whenever they were touched. Except for the decidedly septic appearance of the patient the remainder of the physical examination was essentially negative. Examination of the lungs showed slight impairment of resonance below the fourth right rib, with bronchial breathing and fine crepitant râles. Examination of the heart revealed nothing except tachycardia.

At that time it was thought that he had right lobar pneumonia with septicemia. In view of the significant occupational history, and the presence of the ascending lymphangitis and the epitrochlear and axillary adenitis it occurred to the interne, Dr. H. W. Harris, who examined the patient when admitted, that the diagnosis might be tularemia. The overwhelming character of the infection seemed to be the only argument against such a diagnosis. The writer was called in consultation and concurred in the diagnosis of tularemia. Ten cubic centimeters of blood were withdrawn at this time for guinea pig inoculation and agglutination tests. One cubic centimeter of serum was immediately injected into each of two guinea pigs. The remainder was sent to Francis, at the Hygienic Laboratory, Washington, D. C.

All attempts to reduce the patient's temperature were of no avail. On the morning of the 26th his condition was obviously worse. He became more delirious and it became necessary to employ mechanical restraint. He developed urinary and fecal incontinence, associated with a profuse watery diarrhea. His speech was thick and incoherent and he could be aroused only with great difficulty. The temperature remained at 106°F. until 4:23 P. M. when the patient died, just 24 hours after his admission to the hospital and 4 days and 7 hours after the onset of his illness.

A blood count, made on the morning of the 25th, showed 5,200,000 red blood cells; hemoglobin, 90 per cent; white blood cells, 15,400; differential count: polymorphonuclear neutrophiles 91 per cent and small lymphocytes 9 per cent.

There was some difficulty encountered in obtaining permission for postmortem examination and it was impossible to begin the autopsy until 10:00 o'clock on the morning of November 27. The autopsy findings follow:

F. W.; age, 25; nationality, American negro; occupation, dresser of rabbits and chickens at the J. O. F. market.

Clinical Diagnosis: Pneumonia; tularemia.

External Examination

Build: Body is that of a slender, well developed, negro youth, appearing to be of stated age; body length, 162 cm. *General Nutrition*: Good. *Head*: Symmetrical, no scars or wounds. *Facies*: Symmetrical. *Eyes*: Pupils moderately dilated, round, equal and regular; sclerae clear. *Neck*: A few palpable kidney bean-size lymphnodes in the lower half of the anterior cervical chain. *Thorax*: Symmetrical; intercostal angle less than a right angle. *Abdomen*: Flush with the rib margin. *Back*: Well marked hypostasis over dependent dorsal areas. *Skin*: Fine, soft, relatively inelastic; deeply melanotic; the skin over the right hand from the finger tips to the wrist shows extensive exfoliation, with many deep irregular fissures extending into the corium; no well-defined ulcers; the skin of the fingers of the left hand shows a similar, but

less marked, desquamation. *Hair*: Normal distribution. *Teeth*: Carious; moderate pyorrhea. *Mucous Membranes*: Cyanotic. *Muscles*: Well developed. *Rigor Mortis*: Present over abdomen and lower extremities. *Panniculus*: Practically absent. *Edema*: None. *Body Heat*: Absent. *Mouth*: No ulcers. *Nose*: No perforation. *Ears*: No discharge. *Genitals*: No penile scars. *Anus*: No hemorrhoids or fissures.

Spinal Cord and *Head* not examined because of stated restrictions.

Main Incision

Panniculus: Represented by a few scattered lobules of fat. *Musculature*: Very well developed; the abdominal recti, especially below the umbilicus, show extensive Zenker's necrosis, presenting the typical waxy, hyaline, fish flesh-like appearance. *Abdominal Cavity*: Contains no free gas or fluid. *Omentum*: Gathered loosely about the transverse colon; no adhesions. *Position of Abdominal Organs*: Liver descends one finger's breadth below the rib margin in the midclavicular line; spleen does not descend below the rib margin. *Position of Diaphragm*: Fourth interspace on the right, fifth interspace on the left. *Costal Cartilages*: Elastic, cut with ease. *Sternum*: Abundant red-brown marrow.

Thorax

Thoracic Cavity: Contains no free gas or fluid. *Position of Thoracic Organs*: Normal relationship. *Anterior Mediastinum*: Lymphnodes small. *Thymus*: Replaced by thin sheet of fat; a few slender strands of persistent whitish thymic tissue: *Pericardium*: Smooth, moist and shining; multiple healed "soldiers' spots" over right ventricle; just above the apex the pericardial surfaces are firmly adherent over an area about the size of a silver dollar; sac contains about one tablespoonful of clear yellowish fluid. *Heart*: About the size of the cadaver's right fist; apex in the fifth interspace in the midclavicular line; apex formed entirely by the left ventricle; right border at right parasternal line. *Left Heart*: Wall averages 14 m.m. in thickness; no fibrosis; no infarcts; endocardium pale, yellowish-gray; diffuse fatty degenerative infiltration of subendocardium; marked "tiger heart"; no thromboses; mitral orifice admits two fingers; no vegetations; aortic orifice admits thumb with ease; no vegetations. *Right Heart*: Wall averages 6 m.m.; no fibrosis; no infarcts; diffuse subendocardial fatty degenerative infiltration; tricuspid orifice admits four fingers; no valvular abnormalities; pulmonic ring takes two fingers easily. *Coronary Vessels*: Thin-walled throughout. *Left Lung*: Multiple old firm pleural adhesions; a patch of healed apical tuberculosis about the size of a silver dollar; many healed subpleural tubercles; on section, marked passive congestion; moderate edema; no pneumonia; no active tuberculosis. *Right Lung*: Similar to the left except that in the lower lobe, in the costophrenic thin margin, is a walnut-size, firm, reddish-brown area which on section has the appearance of a recent abscess with a cherry-size necrotic core; in the middle lobe, just beneath the pleura, is a similar cherry-size area surrounded by a zone of purulent infiltration. *Bronchi*: Contain a moderate amount of frothy edema fluid; no purulent exudate. *Bronchial Glands*: Markedly hyperplastic and anthracotic; contain multiple healed and caseous tubercles. *Pulmonary Vessels*: Thin walled; elastic; no thrombi; no emboli. *Aorta*: Hypoplastic; thin walled; elastic; no atherosclerosis; no evidence of syphilis. *Thoracic Portion of Esophagus*: Negative.

Abdomen

Peritoneum: Smooth, moist, and shining throughout; no free gas or fluid. *Spleen*: About one and one-half times normal size; weight, 165 grams; measures 15x9x5 cm.; capsule smooth and shining; beneath the capsule are seen multiple whitish and grayish-white round areas varying in size from pin-head to small pea; on section, similar ones are found throughout the spleen; these do not have the appearance of hyperplastic Malpighian corpuscles or tubercles, but have more the appearance of focal necroses; pulp is rather soft over the cut surface. *Large In-*

testine: No ulcers; mucosa shows marked congestion. *Appendix*: In part retrocecal; arches medially toward the brim of the pelvis; no evidence of inflammation. *Small Intestine*: Marked congestion of mucosa; no ulcers; Peyer's patches small. *Duodenum*: Contains a small amount of bile-stained mucin; no ulcers or scars. *Bile Passages*: Patent. *Stomach*: Slightly distended with gas and a small amount of turbid fluid; no ulcers; no scars; mucosa congested and covered with thin layer of mucin. *Pancreas*: Normal size and consistence. *Liver*: Normal size; capsule smooth and shining; on section, shows rather marked acute congestion and cloudy swelling; no visible whitish focal necroses; no increase of stroma. *Gall Bladder*: Thin walled; mucosa intact; no sand; no calculi. *Portal Vein*: No thrombosis. *Mesenteric Lymphnodes*: Slightly enlarged; no caseous necrosis. *Left Adrenal*: Moderately hypoplastic, particularly in the medulary portion. *Left Kidney and Ureter*: Normal size; capsule strips readily, leaving a smooth congested surface; on section, marked cloudy swelling and passive congestion; pelvis, thin walled; ureter, negative. *Right Adrenal*: Similar to the left. *Right Kidney and Ureter*: Similar to the left. *Abdominal Aorta*: Thin walled; hypoplastic; no atherosclerosis; no evidence of syphilis.

Male Pelvis

Penis: No scars. *Scrotum*: No edema. *Testis*: Soft; no evidence of orchitis fibrosa syphilitica. *Rectum*: Marked passive congestion. *Prostate*: Normal size and consistence; no glandular hyperplasia. *Seminal Vesicles*: Thin walled; moderately distended with seminal fluid. *Urethra*: Negative. *Bladder*: Greatly distended with urine; fundus four fingers' breadth above the symphisis pubis; mucosa shows congestion of trigon.

Special Regional Examination

Lymph Glands: The right epitrochlear lymph glands are moderately enlarged, averaging kidney-bean size. The right axillary nodes are tremendously enlarged, many of them being of plum size. On section, these nodes are very soft, friable, and show extensive caseation.

Microscopic Findings

Axillary and epitrochlear lymphnodes: Multiple focal necroses, miliary and submiliary in size. The necrosis is very recent. The nuclei of the necrotic lymphocytes show karyoschisis and karyorrhexis. Early caseation necrosis. The periphery of the necrotic areas is irregular, but very sharply defined from the neighboring intact lymphocytes. Surrounding these focal necroses there is early fibroblastic and epithelioid proliferation, with marked hyperplasia of the reticulo-endotheliocytes. The epithelioid granulation tissue is devoid of new formed capillaries. The process has been too acute for the development of mature connective tissue. No distinct foreign-body giant cells of the Langhans type are to be seen, although some of the histiocytes have fused to form a kind of symplasm, probably representing early giant cell forms. Alcohol-fixed paraffin sections show no tubercle bacilli by the modified Ziehl-Neelsen method as applied to tissue sections. Smears made from the lymphnodes before fixation showed no acid-fast organisms. A few scattered polymorphonuclear leucocytes at the periphery of the foci of necrosis. Practically no distinct germ centers. The capillaries are widely dilated and engorged with red blood cells. (See Fig. 2.)

Heart: Diffuse subendocardial fatty degenerative infiltration. "Tiger heart." Healed epicarditis.

Lungs: Extreme acute passive congestion, with moderate edema. In the right lung are two areas of caseous necrosis with polymorphonuclear infiltration at the periphery. These suggest tularemic necroses. Healed tubercles. Chronic adhesive pleuritis.

Bronchial lymphnodes: Multiple healed tubercles.

Spleen: Multiple focal necroses, varying in size from pin-point to small pea. The lesions are essentially similar to those found in the axillary nodes. In some low-power fields, eight to ten small foci of necrosis can be gathered into one field. The necroses

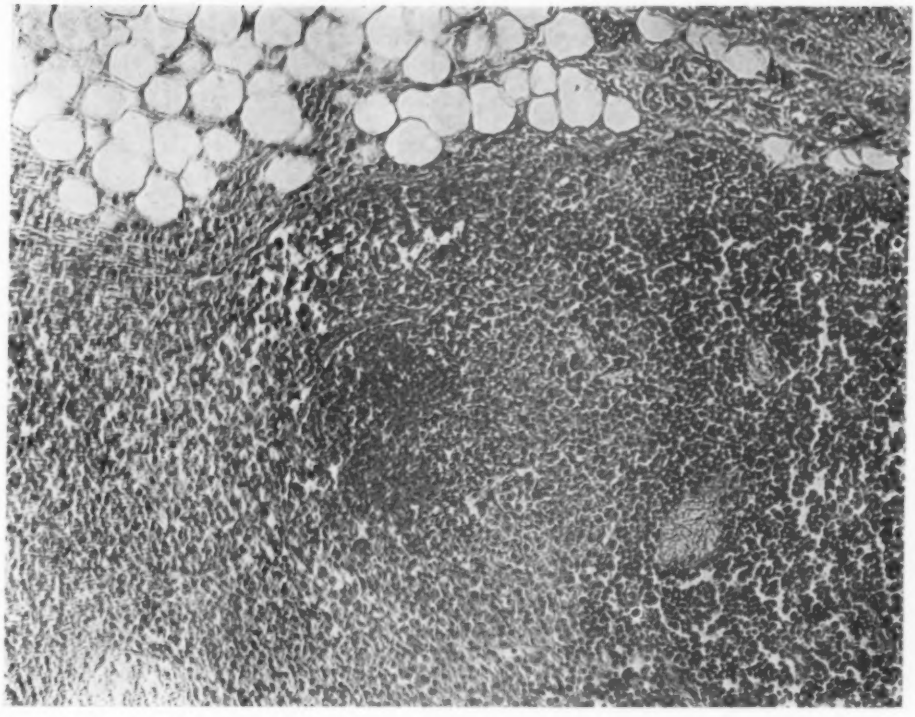

FIG. 2. Mr. F. W. died on fourth day of disease. Photomicrograph of periphery of axillary lymphnode, showing focal necrosis, with early fibroblastic and epithelioid proliferation and hyperplasia of reticulo-endotheliocytes. Intact lymphocytes at right. Perilymphadenitis, involving surrounding axillary fat. No Langhans' giant cells.

involve by far the greater part of practically every low-power field. Malpighian corpuscles show a decided diminution in number of lymphocytes. Intense acute passive congestion. Some of the focal necroses are surrounded by a zone of fibroblastic and epithelioid cells, while others show little or no peripheral reaction. No mature Langhans' giant cell forms. Marked diffuse reticulo-endothelial hyperplasia. (See Fig. 3.)

Liver: A few submiliary focal lesions with rather extensive reticulo-endothelial proliferation. Very little caseation necrosis. Marked cloudy swelling and localized areas of simple necrosis. (See Figs. 4 and 5.)

Stomach: Excessive mucin.

Kidneys: Very marked cloudy swelling and localized simple necrosis, involving chiefly the proximal convoluted tubules. Multiple hyaline casts in collecting tubules. Marked acute passive congestion. No focal necroses. (See Fig. 6.)

Adrenals: Hypoplasia of medulla. Lipoidosis of cortex. No focal necroses.

Striped Muscle (*rectus abdominis*): Marked Zenker's necrosis. Large hyalinized fibers, with very few intact nuclei. Marked difference in eosinophilic staining qualities. Fragmentation of myofibrils. Cohnheim's areas indistinct. Typical intracellular coagulation necrosis. (See Fig. 7.)

PATHOLOGICAL DIAGNOSIS*

Tularemia. Exfoliating dermatitis of

*A more complete pathological study of the early lesions of tularemia in the lymphnodes and viscera will appear in the Archives of Pathology.

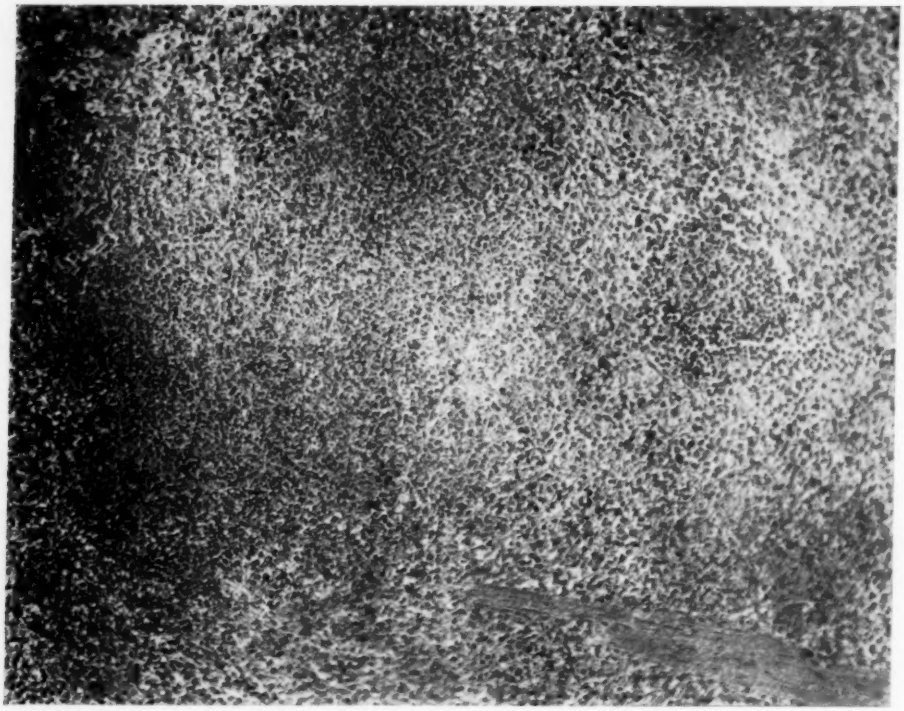

FIG. 3. Mr. F. W. Photomicrograph of spleen, showing multiple foci of necrosis, with early epithelioid and fibroblastic proliferation, and marked reticulo-endothelial proliferation. Marked diminution of lymphocytes in Malpighian corpuscles. No Langhans' giant cells.

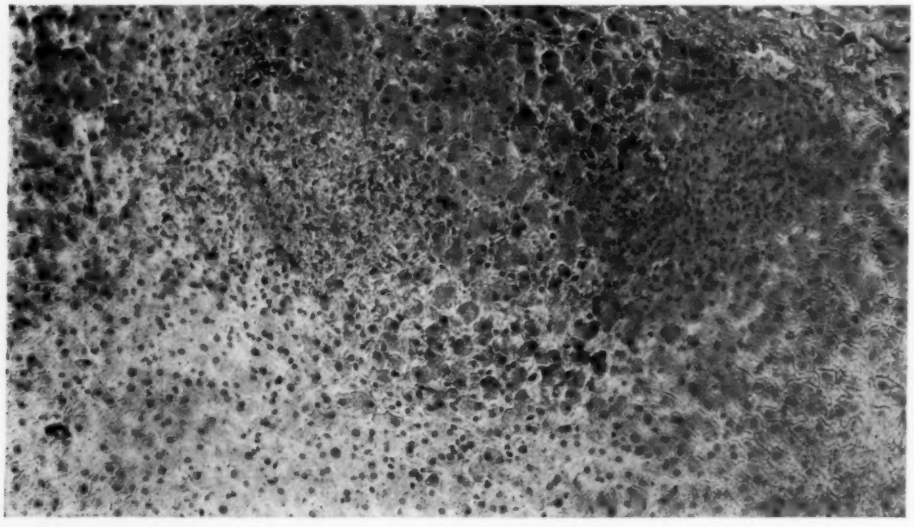

FIG. 4. Mr. F. W. Photomicrograph of two early tularemic lesions in liver. Practically no necrosis, but a marked hyperplasia of reticulo-endothelium. Cloudy swelling of hepatic parenchyma.

hands, most marked on right. Ascending lymphangitis of right upper extremity, with epitrochlear and axillary lymphadenitis. Multiple focal necroses of epitrochlear and axillary nodes, spleen, liver, and right lung. Marked cloudy swelling and localized simple necrosis of liver and kidneys. Subendocardial fatty degenerative infiltration. Healed tuberculosis of lungs and bronchial nodes. Terminal right sided cardiac dilatation with relative tricuspid and pulmonary insufficiency. Pulmonary congestion and edema. Old adhesive pleuritis and pericarditis. Marked Zenker's necrosis of recti abdominis.

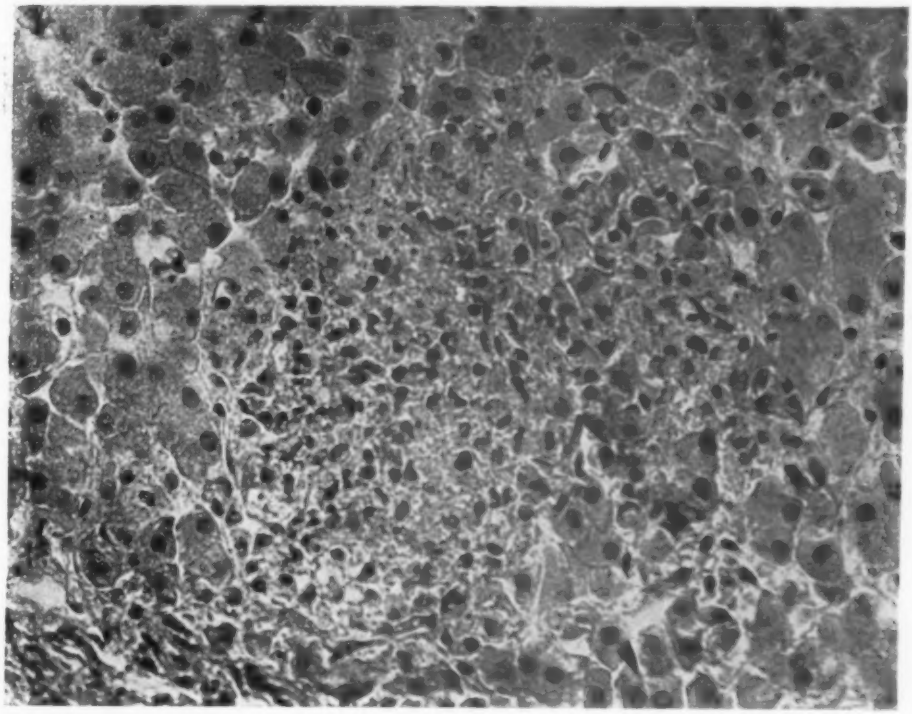

FIG. 5. Mr. F. W. High power photomicrograph of early tularemic lesion of liver, showing marked reticuloendothelial hyperplasia.

This case is by all odds the most rapidly fatal case of tularemia on record (four days, seven hours). Furthermore, the case is unusual in that there is no doubt that tularemia *per se* was the cause of death. In the other fatal cases, of which 23 have been reported, there was usually some contributing factor, such as pneumonia, streptococus septicemia or heart disease.

Immediately after the autopsy, two healthy guinea pigs were inoculated with axillary lymphnode tissue, which had been rubbed up in a mortar, suspended in physiological saline solution, and strained through coarse gauze.

On November 30, the following telegram was received. "Serum negative for tularemia because taken too early in disease. You should exclude tuberculosis. Letter follows. Francis, Hygienic Laboratory."

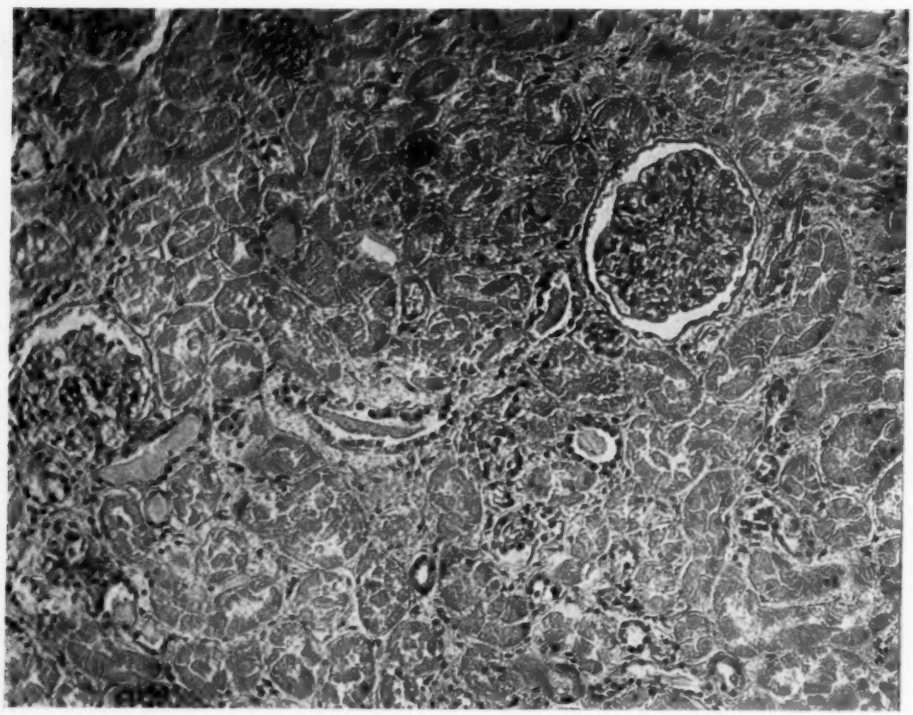

FIG. 6. Mr. F. W. Photomicrograph of cortex of kidney showing cloudy swelling and simple necrosis of the epithelial lining of the proximal convoluted tubules. The nuclei of the epithelium of the distal convoluted tubules are intact. The lumina of many of the distal convoluted and straight tubules contain hyaline tubular casts.

One hour after this telegram was received the first of the two guinea pigs, inoculated with the patient's serum on the afternoon of November 25, died and was autopsied immediately. The characteristic spotted spleen and liver was found, and the heart's blood was placed upon cystine-glucose-peptone-meat infusion agar. In four of the culture tubes the medium was enriched with 5% human serum. Tubes of nutrient agar and broth were likewise inoculated. The remaining pig died during the night of November 30 and December 1 and the same procedures were carried out. Both of the animals inoculated with axillary lymphnode tissue, immediately after the necropsy of F. W., died in four days, with the characteristic gray, granular caseation of the enlarged lymphnodes of the groin, and great numbers of small whitish foci of necrosis in the spleen and liver.

The negative report from Dr. Francis was anticipated, in view of the fact that the blood had been taken on the third day of illness and in the presence of an overwhelming bacteremia. Agglutinins have never been demonstrated in the first week of tularemia.

ticularly since the young man had worked in a wholesale market which had distributed 12,000 rabbits to the markets of the city during the preceding week. It was learned that the rabbits purchased by the company for which F. W. worked had been procur-

FIG. 7. Mr. F. W. Photomicrograph of voluntary muscle of rectus abdominis, showing intracellular hyaline or coagulation necrosis of fibers and absence of nuclei. Typical Zenker's necrosis.

The writer was invited to give a discussion on tularemia before the Montgomery County (Ohio) Medical Society, on Friday evening, December 2. The findings in the fatal case were given, together with an historical sketch of the disease, and it was pointed out that in view of the occurrence of this fatality from tularemia there must be other cases in the city, par-

ed at Maysville and Cynthiana, Kentucky. There is a state law which prohibits the sale of rabbits killed in Ohio. Consequently most of the rabbits sold in this State during the rabbit season are shipped from Kentucky.

On the day following this discussion, six cases were reported to the writer, all of which were proved to be tularemia.

All of the cystine agar cultures, made on November 30, showed the first growth of the characteristic grayish-white small circular colonies on December 3. There was no growth on the nutrient agar medium or in broth. The culture on the cystine agar enriched with human serum was more luxuriant than that on the cystine-glucose-meat infusion-peptone agar. Sterile salt solution suspensions of the organism were injected into three healthy guinea pigs. The guinea pigs thus inoculated died in four days with the characteristic tularemic lesions, and the organism was again recovered from the heart's blood and splenic tissue. Similar animal inoculations were carried out with the material from the remaining guinea pigs originally inoculated, with the same result. The organism was then passed through four series of animals. In each instance the cultures recovered from the animals were taken off in two-tenths per cent formalin and used as an antigen for agglutination against known anti-*tularense* serum. In each instance the organisms agglutinated out promptly to the full titre of the serum.

The hair was shaven from the abdomen of four guinea pigs and the abraded skin was rubbed lightly with pieces of spleen from animals recently dead of tularemia. All of the animals thus treated developed the disease and died within four or five days. The autopsy showed the characteristic gross lesions and in each instance the organism was recovered from the dead animals. Splenic tissue was then rubbed lightly on the unshaven, unabraded, *intact* skin of the abdomen of four guinea pigs. Two of the animals died, one on the fifth day and one on the sixth day, with the characteristic gross lesions; from both the organism was recovering, thus demonstrating that the organism will penetrate unbroken skin.

Tiny fragments of splenic tissue taken from animals recently dead of tularemia were placed in the right conjunctival sac of two healthy guinea pigs. Both animals showed excessive lacrimation on the following day. On the third day there was a grayish-white thin film over the entire conjunctival surface, with marked capillary injection and multiple minute ulcers. Both animals died on the fifth day, with characteristic visceral lesions and caseous regional lymphnodes.

Spleens from the autopsied animals were dropped into tubes containing sterile glycerine and placed in the ice box. Two months after they had been first placed in the ice box, two of the spleens were ground up in a mortar, suspended in physiologic saline solution, and strained through gauze. Two animals were inoculated with the material and both developed the disease, thus demonstrating the extraordinary resistance of this organism.

In view of the large number of infections with *Bacterium tularense* among laboratory workers the greatest caution was exercised throughout all of the experimental work. The animals were immersed in ten per cent formalin solution before autopsy. Sterile gowns, sterile gloves, masks and glasses were worn. All tissues were handled with sterile instruments. All materials used were sterilized immediately after the autopsy and the benches on which the work had been carried out were wash-

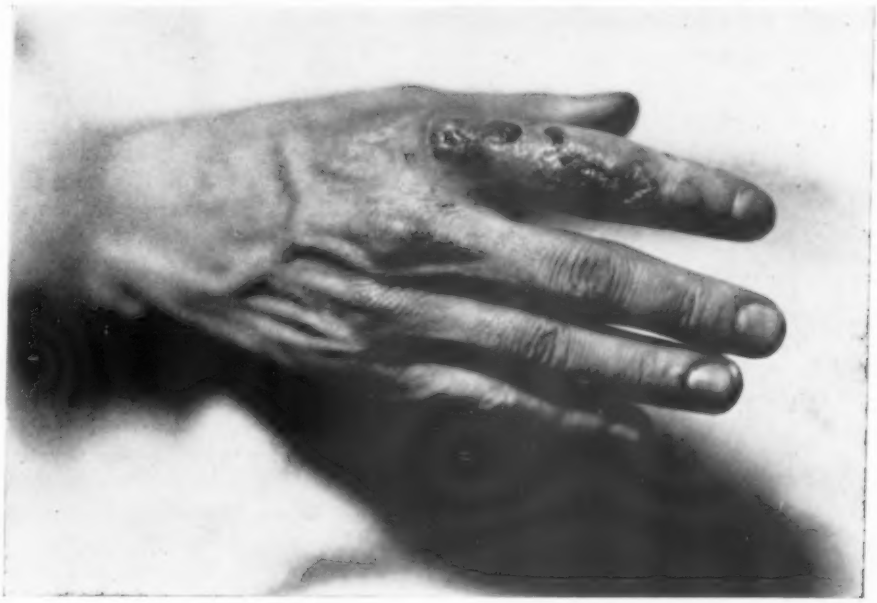

FIG. 8. Mr. H. C., case XIX. Primary lesion of right index finger, overlying proximal interphalangeal articulation, after incision. Nodular lymphangitis overlying metacarpophalangeal articulation. Photograph taken 6 weeks after onset.

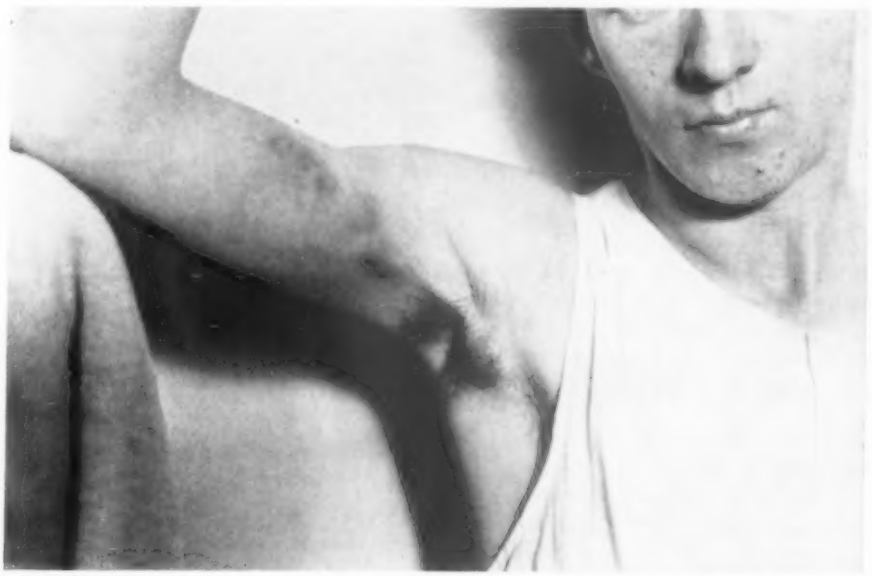

FIG. 9. Mr. H. C., case XIX. Axillary adenopathy and sporotrichosis-like nodular lymphangitis of upper arm. Six weeks after onset.

ed off with ten per cent formalin solution. The hands were washed with soap and water, then immersed in ten cent formalin solution for a few moments and then held under running water. The cages in which the animals died were immersed in boiling water. No person engaged in the experimental work in our laboratory contracted the disease.

On December 13 the following letter was received:

TREASURY DEPARTMENT
UNITED STATES PUBLIC HEALTH SERVICE
WASHINGTON, D. C.

December 12, 1927

Hygienic Laboratory
Twenty-Fifth and E. Streets NW.

Dr. W. M. Simpson, Pathologist,
Miami Valley Hospital,
Dayton, Ohio.

Dear Doctor Simpson:

Serum of Felton Williams, on which I reported negative agglutination November 30th was injected November 29th subcutaneously into pig No. 1 and intraperitoneally into pig No. 2. Pig No. 1 was killed while dying December 5th and showed the typical lesions of tularemia—caseous lymph nodes and spotted spleen and liver. Pig No. 2 died December 2nd, showing no gross lesions of lymph nodes, but showed the spotted spleen and liver.

Cultures of heart blood of pig No. 2, taken at moment of death, showed growth December 4th from which a transfer was made December 5th. The latter was taken off in 0.2% formalin and used December 11th as an antigen for agglutination against a known anti-*tularense* serum, a known tularense organism being also set up in the agglutination test. Both organisms agglutinated out promptly to the full (1:1280) titre of the serum.

Transfers from the spleen of pig No. 2, to the shaven abraded skin of the abdomen of two pigs caused their death December 6th and they showed the typical lesions of tularemia—caseous lymph nodes and spotted spleen and liver.

Your case is the most rapidly fatal (5 days) of any on record. The next shortest are the family group which died in Virginia on the 6th, 8th and 8th days, respectively; the next is the case which died August 9, 1927, at St. Mary's Hospital, Duluth, Minnesota, on the 13th day; the next is the case which died December 8, 1927, on the 14th day, at the United States Naval Hospital, Washington, D. C.

I admire the way you have attacked the situation, but I must warn you that if you continue to autopsy infected pigs you are sure to go to the hospital—there have been 20 laboratory infections of man in 5 laboratories in this country, in England and in Japan.

Sincerely yours,
Edward Francis, Surgeon.

Non-Fatal Cases

A. 1927 Cases

When the cause of death in the case of F. W. was established, our attention ws directed to the other rabbit dressers at the J. O. F. market. It soon developed that eight other rabbit handlers at this market were acutely ill. All of the rabbits dressed at this market had been received from Maysville and Cynthiana, Kentucky. Rabbits shipped to Dayton from Kentucky, Missouri and Kansas have been responsible for all but five of our cases. In these five instances, the disease resulted from contact with rabbits killed in the woods near Dayton. Within the next two months the writer saw 24 persons who were suffering from the disease. All of the persons involved in the 1927 epidemic developed the disease during November. In no case did the disease result from contact with domestic rabbits. This is

in keeping with the experience of other investigators.

Case I

Mr. W. S., age 49, dressed rabbits at the J. O. F. market on November 24, 1927. He had previously dressed chickens and had acquired several fissures in the skin of both hands as a result of constant immersion in hot water. On November 26, he was taken suddenly ill with chills, severe headache and throbbing pain in the left hand. At the same time he noticed a painful mass in the left axilla which rapidly reached the size of a lemon. His fever reached 103°F. and he was delirious for one week. He was confined in bed for 16 days. The axillary mass was incised and drained. It was 12 weeks from the time of the onset of his illness before Mr. S. was able to return to his work. He still complains (February 29) of great weakness.

Serum of Mr. S., taken on December 9, 1927, was found by Francis to agglutinate *Bacterium tularense* in all dilutions to 1:160.

Case II

Mr. L. H. F., age 43, dressed rabbits at the J. O. F. market on the day before Thanksgiving, 1927. He perforated the skin of the pad of the right thumb with a sharp needle-like fragment of rabbit spine. One drop of blood escaped after the perforation. On the Saturday after Thanksgiving, he experienced chills, a fever which went to 101°F. and he noticed for the first time a painful swelling in the right axilla which assumed the size of a small lemon. At the same time he noticed an English walnut size mass in the left axilla, with ascending reddish streaks on both arms. Shortly after this he noticed a small papule at the point of injury to his thumb which rapidly developed into a dime-size ulcer. The primary lesion was incised on the following day. Mr. F. remained in bed for four weeks. The axillary mass was not incised nor did it drain spontaneously. Mr. F. was unable to return to his work until February 3, 1928. He still feels very weak.

Serum of Mr. F., submitted to Francis on December 18, 1927, was found to agglutinate *Bacterium tularense* in all dilutions to 1:640.

Case III

Mr. E. B., age 43, had dressed rabbits and chickens at the J. O. F. market since the beginning of the rabbit season, November 15, 1927. While dressing chickens he had immersed his hands for long periods in hot water and had acquired several small fissures. On November 30, 1927, he developed chills and fever and a severe headache. Even though his doctor, Clement Fischer, insisted that he go to bed he refused to do so for any length of time. The right axillary mass assumed the size of a lemon. After it became fluctuant it was incised. Mr. B. returned to his work on January 9, 1928, still feeling very weak.

Serum of Mr. B., collected on December 17, 1927, was found by Francis to agglutinate *Bacterium tularense* in all dilutions to 1:160.

Case IV

Mrs. D. S., age 45, patient of Dr. Clement Fischer, dressed rabbits at the J. O. F. market. On November 25, she perforated the little finger of the left hand with a sharp fragment of rabbit bone. Three days later she was taken suddenly ill with a severe chill and a rapid elevation of tempertaure to 103°F. She suffered severe headache and aching pains in the extremities and back. A walnut size mass appeared in the left axilla. She was confined to bed at St. Elizabeth's hospital for six weeks. She returned to her home where she was forced to lie down most of the time, quite unable to do any work. On February 25, 1928, she was readmitted to St. Elizabeth's hospital for the surgical drainage of a left axillary abscess which had extended beneath the pectoralis major muscle. She was confined to bed at this time for three weeks. She is still very weak and unable to do the duties to which she is accustomed.

Serum of Mrs. S., taken on December 18, 1927, was found by Francis to agglutinate *Bacterium tularense* in all dilutions to 1:160.

TABLE I
1927 Cases

Case No.	Initials	Sex	Age	Occupation	Source of Infection	Primary Lesion	Incubation Period	Onset Date	Adenopathy	Suppuration	Agglutination (by Francis)	Convalescence	Type
1	F.W.	M	25	Poultry and rabbit dresser, J. O. F. market	Kentucky rabbits	Multiple fissures of right hand. No ulcer.	Unknown	Nov.22,1927	Right epitrochlear and axillary	None	Proved by animal inoculation	Died, 4 days after onset	G
2	W.S.	M	49	Poultry and rabbit dresser, J. O. F. market	Kentucky rabbits	Multiple fissures	2 days	Nov.26,1927	Left axillary	Incised	1:160	Twelve weeks plus	G
3	L.H.	M	43	Poultry and rabbit dresser, J. O. F. market	Kentucky rabbits	Right thumb	3 days	Nov.23,1927	Right and left axillary	None	1:640	Four weeks plus	UG
4	H.B.	M	43	Poultry and rabbit dresser, J. O. F. market	Kentucky rabbits	Multiple fissures	Unknown	Nov.30,1927	Right axillary	Incision	1:160	Five weeks plus	G
5	D.S.	F	45	Poultry and rabbit dresser, J. O. F. market	Kentucky rabbits	Left little finger	3 days	Nov.25,1927	Left axillary	Incised	1:320; partial 1:640	Four months plus	UG
6	H.H.	M	23	Poultry and rabbit dresser, J. O. F. market	Kentucky rabbits	No ulcer	3 days	Nov.25,1927	Left axillary. Nodular lymphangitis.	Incised	1:640; partial 1:1280	Two months	G
7	A.B.	F	46	Poultry and rabbit dresser, J. O. F. market	Kentucky rabbits	Left middle finger	2 days	Nov.23,1927	Left epitrochlear and axillary. Nodular lymphangitis	None	Tularense, 1:1280 Abortus, 1:320 Melitensis,1:320	Two months	UG
8	C.F.	M	42	Poultry and rabbit dresser, J. O. F. market	Kentucky rabbits	Left index finger	2 days	Nov.24,1927	Left axillary. Nodular lymphadenitis.	Incision	1:1280	Four weeks	UG
9	C.A.	M	20	Poultry and rabbit dresser, J. O. F. market	Kentucky rabbits	Left thumb	Indefinite	Nov.20,1927	Left axillary, right epitrochlear	Incision of right epitrochlear mass	1:640	Three months plus	UG
10	J.K.	M	40	Meat cutter	Kentucky rabbits	Palmar surface of right hand	3 days	Nov.23,1927	Right epitrochlear and axillary	None	1:640	Two months plus	UG
11	P.J.	M	52	Realtor	Kentucky rabbit	Left ring finger	4 days	Nov.27,1927	Left axillary. Nodular lymphangitis.	None	1:640; partial 1:1280 Abortus, 1:40	Eight weeks	UG
12	A.B.	F	50	Housewife	Local rabbit	Right thumb	Seven days	Nov.26,1927	Right axillary	None	1:160		UG
13	A.K.	M	20	Meat cutter	Kentucky rabbits	Right thumb	2-6 days	Nov.26,1927	Right axillary	Incision	1:2560	Three weeks	UG
14	C.W.	F	36	Housewife	Local rabbit	Right middle finger	Two days	Nov.25,1927	Right axillary and epitrochlear	Incision	1:1280		UG
15	I.S.	F	50	Housewife	Kentucky rabbit	Right thumb	Two days	Nov.24,1927	Right epitrochlear and axillary	None	1:2560	Four months plus	UG
16	J.S.	M	38	Commission merchant	Kentucky rabbits	Left index finger. Right thumb.	Four days	Nov.26,1927	Left epitrochlear and axillary. Right epitrochlear and axillary.	Excision	1:2560	Five months plus	UG
17	C.M.	M	22	Farmer	Kentucky rabbits	Web between right thumb and index finger	Four days	Nov.26,1927	Right axillary	Spontaneous	1:1280	Six weeks	UG
18	A.E.	M	65	Farmer	Kentucky rabbits	Fourth finger right hand	Four days	Nov.26,1927	Right axillary	None	1:1280	Six weeks	UG
19	F.C.	M	40	Farmer	Kentucky rabbits	Fourth finger right hand	Four days	Nov.26,1927	Right epitrochlear. No axillary.	None	Tularense,1:640 Abortus, 1:80 Melitensis,1:80	Four weeks	UG
20	H.C.	M	20	Poultry and rabbit dresser	Kentucky rabbits	Index finger right hand	Four days	Nov.25,1927	Right axillary. Nodular lymphangitis.	Excision	1:1280	6 months plus	UG
21	C.P.	M	25	Poultry and rabbit dresser	Kentucky rabbits	Right thumb	Four days	Nov.21,1927	Right axillary	None	1:320	Rapid	UG
22	A.G.	M	34	Grocer	Kentucky rabbits	Right middle finger	Two days	Nov.20,1927	Right axillary	Excision	1:1280	8 months plus	UG
23	W.M.	M	67	Retired farmer	Local rabbits	Web between left thumb and index finger; also left right finger.	Two days	Nov.18,1927	Left axillary	None	1:160	Two months	UG
24	M.H.	F	42	Housewife	Kentucky rabbit	Right thumb	Two days	Nov.30,1927	Right epitrochlear. No axillary	None	1:1640	8 weeks plus	UG

G = Glandular type UG = Ulceroglandular type

Case V

Mr. H. H., age 21, dressed rabbits at the J. O. F. market on November 22, 1927. Three days later he was taken suddenly ill with chills, high fever, and large painful glands in the left axilla. The index finger of the left hand was swollen but there was no ulcer. Dr. Clement Fischer made the diagnosis of glandular type of tularemia. Just above the bend of the elbow in the inner bicipital grove a walnut size nodule developed. This nodule was later incised by Dr. Fischer. The axillary mass did not break through the skin nor was it surgically drained. Mr. H. remained in bed for two weeks and was unable to return to his work for two months.

Serum of Mr. H. taken on December 17, 1927, was found by Francis to agglutinate *Bacterium tularense* in all dilutions to 1:640 with partial agglutination at 1:1280.

Case VI.

Mrs. A. A. B., age 40; helper at J. O. F. market; patient of Dr. Clement Fischer. On Friday night, November 18, and on Monday night, November 21, 1927, Mrs. B. dressed rabbits. On Monday evening she stuck the sharp edge of a rabbit bone into the lateral aspect of the distal phalanx of the dorsal surface of the middle finger of the left hand, near the finger nail. The next day there developed a "run around" (paronychia). On Wednesday evening she experienced a severe chill followed by a drenching sweat, and accompanied by high fever and severe aching pains all over the body. At this time she noticed a dozen small nodules along the lymphatics of the forearm, with a walnut size nodule over the inner aspect of the biceps at the junction of the proximal and middle thirds of the arm. Two small cherry sized left epitrochlear swellings developed, together with a hen's egg size mass in the left axilla. Two days later (November 25) she was admitted to St. Elizabeth's hospital with an admission temperature of 105°F. She was delirious from the time of the onset of her illness, on Wednesday, until the following Sunday. On Monday, November 28, the finger lesion was lanced by a physician. The chills, sweats, fever and prostration continued during her nine days' stay in the hospital. After she returned to her home she was compelled to lie down most of the time for three weeks. Since that time she has been very weak and unable to do her accustomed amount of work. The axillary mass was not surgically incised nor did it rupture spontaneously. When examined by the writer on February 27, 1928, a walnut size firm mass was present in the axilla and several small firm nodules along the lymphatics of the forearm and one cherry size firm nodule in the arm.

Serum of Mrs. B., taken on December 17, 1927, was found by Francis to agglutinate *Bacterium tularense* in all dilutions to 1:1280, *Bacterium abortum* in all dilutions to 1:320, and *Bacterium melitense* in all dilutions to 1:320. A second specimen, taken January 10, 1928, agglutinated these three organisms in the same titre as previously found. A third specimen, collected on February 27, 1928, agglutinated *Bacterium tularense* in all dilutions to 1:640.

Case VII

Mr. O. E. F., age 42; poultry and rabbit dresser at the J. O. F. market. On the 20th of November, 1927, Mr. F. scratched the skin of his left index finger over the medial aspect of the distal phalanx with a piece of ice. Two days later he dressed rabbits. On Thanksgiving day, two days after dressing the rabbits, he experienced an excruciatingly severe headache, accompanied by chills and fever. In the middle of the flexor surface of the left forearm a hickory nut size mass developed on Thanksgiving day. The next day he first noticed a similar mass over the inner aspect of the left arm in the groove between the biceps and triceps. These became exquisitely painful, and the one in the arm was lanced by a physician. When seen by the writer on February 8, 1928, the nodule in the midforearm was about the size of a hickory nut and covered by very thin skin, and looked to be on the point of spontaneous rupture. At no time did Mr. F. suffer from any

axillary pain, although he complained of some difficulty in elevating the arm above the level of the shoulder. On deep palpation a cherry-size firm node was found in the left axilla. Mr. F. took to his bed on Thanksgiving day and remained there for four weeks, during which time he lost 28 pounds. He is quite active now, although he complains that he does not feel as well as he did before the onset of this illness.

Francis reported that the serum taken on February 8, 1928, from Mr. F., agglutinated *Bacterium tularense* in all dilutions to 1:1280.

Case VIII

Mr. C. A., age 20; poultry and rabbit dresser at the J. O. F. market. Mr. A. dressed rabbits for ten days before Thanksgiving, 1927. He had an old, unhealed knife-cut on the left thumb just above the nail. The day before Thanksgiving he became acutely ill with a high fever (104.5°F.). He suffered from severe headache, pains in the back and extremities, chills and sweats. On Thanksgiving day he noticed for the first time a painful swelling in the left axilla which, during the next week, assumed the size of a lemon. At the same time that the left axillary mass developed a similar mass appeared in the *right* epitrochlear nodes which rapidly assumed the size of a hen's egg. He applied flax seed poultices to both masses. The right epitrochlear mass was drained surgically, 14 days after the onset of his illness. The left axillary mass "came to a head and broke." A small ulcer developed at the site of the old knife cut. He remained in bed for fifteen days during which time the fever persisted. To date, February 26, he has been unable to return to his work because of extreme weakness.

Serum of Mr. A., collected on February 15, 1928, was found by Francis to agglutinate *Bacterium tularense* in a dilution of 1:640.

Case IX

Mr. J. K., age 40, a butcher at the S. market scratched his hands in many places while dressing rabbits three days before Thanksgiving, 1927. These rabbits had been received from Kentucky. On the day after Thanksgiving his hand became swollen and there developed distinct reddish-blue streaks along the lymphatics of the right upper extremity and he very rapidly developed large and very painful lymphnodes in the axilla and in the epitrochlear area. Several of the epitrochlear nodes were of kidney bean size while the axillary mass was the size of an English walnut. He developed a fever of 103.5°F., together with a moderate leucocytosis (12000). In the center of the right palm the writer found a reddish papule, 1 cm. in diameter. This had been incised by a family doctor on the day after Thanksgiving; no purulent exudate escaped, and the patient felt worse after the incision. This was the first case to be recognized clinically in Dayton after the fatal case. The correct diagnosis was made by Dr. E. E. Bohlender.

A blood specimen, collected on December 2, was found to agglutinate *Bacterium tularense* in dilutions of 1:2, 1:5, and 1:10. This was in accord with the results anticipated with a serum collected on the ninth day of illness. An attempt was made one week later to obtain a second specimen but it was found that the patient had disappeared from the city. He was located in Cincinnati, on February 28, 1928. Serum collected on this date was found by Francis to be positive in all dilutions to 1:640.

Case X

Mr. P. S. J., age 52; real estate salesman; patient of Dr. H. F. Koppe. Mr. J. purchased a rabbit in the Arcade market on November 21, 1927. It had already been skinned and dressed. The only contact with the rabbit occurred while Mr. J. was cutting the rabbit into small pieces preparatory to cooking. He did not cut or scratch himself during the process. On November 27 he had a rather severe chill and felt that he was acquiring "grippe." The chill was followed by an elevation of temperature, and Dr. Koppe was called. He found the temperature to be 103°F., pulse 120. The patient complained of chilly sensations and of generalized aching pains all over, but espe-

cially marked in the back of the neck. The patient felt certain that he had the "grippe." On physical examination, there was a small reddened area adjacent to the nail on the ring finger of the left hand. This had the appearance of an infected hang nail. There was slight enlargement of the left axillary lymphnodes. Over the abdomen, thighs and scrotum was a maculo-papular eruption. On December 3 the patient was able to come to Dr. Koppe's office, where it was found that the axillary mass had reached lemon size and that the lymphatics in the internal bicipital furrow were reddened and indurated, with two nodular swellings just above the inner condyle of the humerus. Weakness was the most marked symptom. During this period the temperature fluctuated from 98° to 101°. On December 15 blood was taken to confirm the clinical diagnosis of tularemia.

Francis found that the serum agglutinated *Bacterium tularense* in all dilutions to 1:320, but not in higher dilutions. On December 19, a second specimen was sent which agglutinated *Bacterium tularense* in all dilutions to 1:640, with partial agglutination at 1:1280. The later specimen also cross-agglutinated *Bacterium abortum* (1:40). The patient remained in bed until December 21 when he returned to his work, still feeling very weak. There has been little diminution in the size of the axillary mass or in the nodules along the lymphatics of the arm but they are not painful and show no signs of rupture (see photographs).

Case XI

Mrs. A. B., age 50; housewife; patient of Dr. V. E. Hutchens. Mrs. B. prepared a rabbit for cooking at her home. The rabbit had been killed on November 19th, 1927, in the woods of Adams County, Ohio. Soon after preparing the rabbit Mrs. B. noticed an abrasion upon her right thumb. This remained slightly sore for about seven days when the thumb became greatly swollen and extremely painful. At this time she experienced slight chills. Dr. Hutchens was called on the ninth day of her illness, when he found a temperature of 100°F. and the pulse of 108. There was a large papule on the right thumb, and the right axillary nodes were enlarged to the size of a large cherry and were very tender; there were no palpable epitrochlears. The patient states that her fever commenced seven days after the injury to her thumb. The center of the papule broke down, the central necrotic core sloughed out, leaving an ulcer ¼ inch in diameter with a deep necrotic base. The axillary glands have, to date, shown no tendency to suppurate.

A blood specimen was taken twelve days after the development of the fever, and Francis reported that the serum agglutinated *Bacterium tularense* in all dilutions from 1:10 to 1:160, thus confirming the diagnosis of tularemia. A guinea pig inoculated with 1 c.c. of serum died in five days with the characteristic caseous inguinal nodes and spotted liver and spleen. The organism was recovered on our human serum modification of Francis' medium.

Case XII

Mr. A. K., age 20; meat cutter at the K. grocery. Mr. K. dressed rabbits, received from the J. O. F. market, during Thanksgiving week, 1927. On November 26 he felt that he was "coming down with the grippe" but went to work. He noticed for the first time, on that day, a small reddish papule on the inner aspect of the pad of the right thumb. After returning from work that day he had a severe chill, and he noticed for the first time painful swelling of the right axillary nodes, so much so that he was unable to raise the right arm. The next day he visited Dr. Raymond Lewis, who recognized the case as one of tularemia. The temperature at this time was 100°F., pulse 100. He was unable to work for two weeks most of which time was spent in bed. The axillary swelling reached lemon size and was surgically incised, two weeks after the onset of his illness. The patient returned to work at the end of three weeks but felt very weak during the following three months.

A specimen was sent to Francis on December 19 and he found that the serum ag-

FIG. 10. Mr. J. S., case XV. Healing ulcer of left thumb, just above nail. Six weeks after onset.

FIG. 11. Mr. J. S., case XV. Two healing ulcers on medial aspect of right index finger. Six weeks after onset.

glutinated *Bacterium tularense* in dilution of 1:2560. A second specimen was sent on February 15, 1928, and it was found to be positive in the same dilution.

Case XIII

Mrs. C. M., age 36; housewife; patient of Drs. Bowers, Arn and Huston. On November 23, Mrs. M. dressed rabbits which had been killed in the woods near her home at Waynesville, Ohio. She scratched the middle finger of the right hand while dressing the rabbits. Two days later she noticed a painful lump in the bend of the right elbow and in the right armpit. There was no visible ascending lymphangitis and she states that she did not suffer from chills or fever. The enlarged lymphnodes became very painful and on December 20 were surgically drained, followed by relief of the pain. Mrs. M. declares that she noted white spots on the liver and spleen of one rabbit which she dressed. Mrs. M.'s serum was found to agglutinate *Bacterium tularense* in all dilutions to 1:1280 (Francis).

Case XIV

Mrs. I. S., age 50; housewife; patient of Dr. E. E. Bohlender. Mrs. S. dressed a Kentucky rabbit, purchased at a local market, on Tuesday, November 22, 1927. At 11:00 P. M., on November 24, she experienced a severe headache with aching pains in the back and extremities. Her temperature rose to 103°F. Dr. Bohlender saw the patient for the first time on December 9, 1927, and found a small ulcer at the tip of the right thumb, together with painful enlargements of the right epitrochlear and right axillary lymphnodes. She was prostrate for five weeks after which she was able to sit up for a few hours at a time. She has not yet (February 26, 1928) regained her strength. The ulcer on th thumb has healed; there is still an English walnut size painful axillary mass whicl has not suppurated. The patient lost an indeterminable amount of weight during her illness but is now regaining it.

Serum sent to Francis on December 29 was found to agglutinate *Bacterium tularense* in all dilutions from 1:10 to 1:25[illegible].

Case XV

Mr. J. S., age 38; commission merchant. On the Monday before Thanksgiving, 1927, he drove his truck to Cynthiana, Kentucky, and purchased 500 rabbits from various grocers. These had been shot by Kentucky hunters and eviscerated in the field. Mr. S. states that the rabbit hunters in Kentucky have learned to have great fear of what they term "rabbit disease" and are cautious about handling the viscera of the rabbits which they kill. They make a practice of making one longitudinal slit with a sharp knife in the mid-line of the abdomen and thorax and then, grasping the rabbit firmly by the hind legs, shake the viscera from the animal. One of the market men, from whom Mr. S. purchased most of his rabbits, threw in a dozen extra rabbits which had been lying around the market for several days, as a "gift."

Mr. S. brought his truckload of rabbits to a farm three miles from Franklin, Ohio, where he and three other men (C.D.M., A.W.E., and F.C.) skinned and partially dressed the 500 rabbits on Tuesday afternoon, November 22. On the Saturday afternoon following Thanksgiving (November 26, 1927) all four of these men became acutely ill within one hour. Mr. S. was forced to take to his bed on Saturday afternoon with "grippe-like" symptoms, a fever which rapidly mounted to 104.5°F. and severe aching pains in the extremities and back. He suffered from repeated chills and sweats. Two days after he took to his bed, he noticed two ulcers on the medial aspect of the right index finger and on ulcer on the left thumb just above the nail (see photographs). Just prior to this observation, he began to experience painful swellings in both axillae but much more marked on the right. The mass in the right axilla reached orange size in one week and became exquisitely painful, so that movements of the right upper extremity were practically impossible. Three cherry sized painful nodes appeared in the left

axilla. In both anticubital fossae enlarged epitrochlears appeared.

Just prior to Thanksgiving day, Mr. S. had distributed about 250 of his rabbits to various Dayton markets, but he discovered, to his dismay, that there was no demand for rabbits in Dayton, because of the publicity which attended the death of F. W. Consequently, on December 1, the fifth day of his illness, he got out of bed, even though he was in a very much weakened condition, and drove to Middletown and Franklin, Ohio, in an endeavor to dispose of the remaining rabbits, which he had placed in cold storage in the interim. He became so sick on this trip that he was forced to abandon the trip and his wife, who accompanied him, drove him home. He remained in bed until January 2. When seen by the writer on January 10, when he was admitted to the Miami Valley Hospital, he was extremely weak and showed evidence of considerable loss of weight, but was without febrile symptoms. The axillary masses had become fluctuant and surgical drainage was advised. Over the upper extremities and neck was found a diffuse maculo-papular eruption. On January 16, 1928, the axillary abscesses were drained and the suppurating lymphnodes were excised by Dr. H. H. Herman. Material from the lymphnodes, including fragments from the abscess walls, was placed upon our human serum modification of Francis' culture medium. Three guinea pigs were inoculated with similar material. On the third day following the inoculation of the culture media the first growth of the characteristic small spherical whitish colonies was noticed (see photograph). The next day these cultures were taken off with sterile saline solution and injected into three guinea pigs. The animals injected directly with the material from the abscesses, and the animals injected with the bacterial suspension died within five days with typical gross lesions of tularemia. From the heart's blood of two of the animals which had been injected with the culture the organism was again recovered, and when injected into two new animals caused death in four days in one instance and in five days in the other To further prove that the organism was *Bacterium tularense*, agglutination tests were carried out with sera from J.S., C.D.M and Mrs. C.M. The organisms agglutinated promptly in all dilutions up to 1:1280.

Mr. S. remained in the hospital for two weeks, after which he returned to his home feeling somewhat better. The drainage continued from the left axilla for one week and from the right axilla until February 25. The patient is still weak and unable to do any physical work (March 3, 1928).

The serum of Mr. S. was found by Francis to agglutinate *Bacterium tularense* in all dilutions to 1:2560. Mr. Fred Berry, Chief of Division of Laboratories, Ohio Department of Health, at Columbus, found that the serum of Mr. S. agglutinated *Bacterium tularense* in the highest titre he made, 1:1230.

Case XVI

Mr. C. D. M., age 22; farmer. For several years, Mr. M. has made yearly trips to Kentucky, during November, to obtain rabbits for Dayton, Ohio, markets. He accompanied Mr. S. (case No. XV) one week before Mr. S. made the trip in which he obtained the 500 rabbits which caused the disease in four people. On this trip, Mr. M. purchased 300 rabbits at Carlisle, Kentucky. These he skinned and dressed and distributed to Dayton markets without untoward event. When Mr. S. returned from Kentucky with the 500 rabbits mentioned above, on November 22, 1927, Mr. M. assisted in the preparation of the rabbits for market. While dressing the rabbits, Mr. M pricked the skin in the web between the right thumb and index finger, on the palmar surface, with a sharp fragment of rabbit bone. On the Saturday afternoon after Thanksgiving, 1927, he developed a high fever, chills and sweats, pains in the back and extremities and noticed a painful swelling in the right axilla. The next day he noticed a reddish papule at the site of the bone prick. In two days this became a

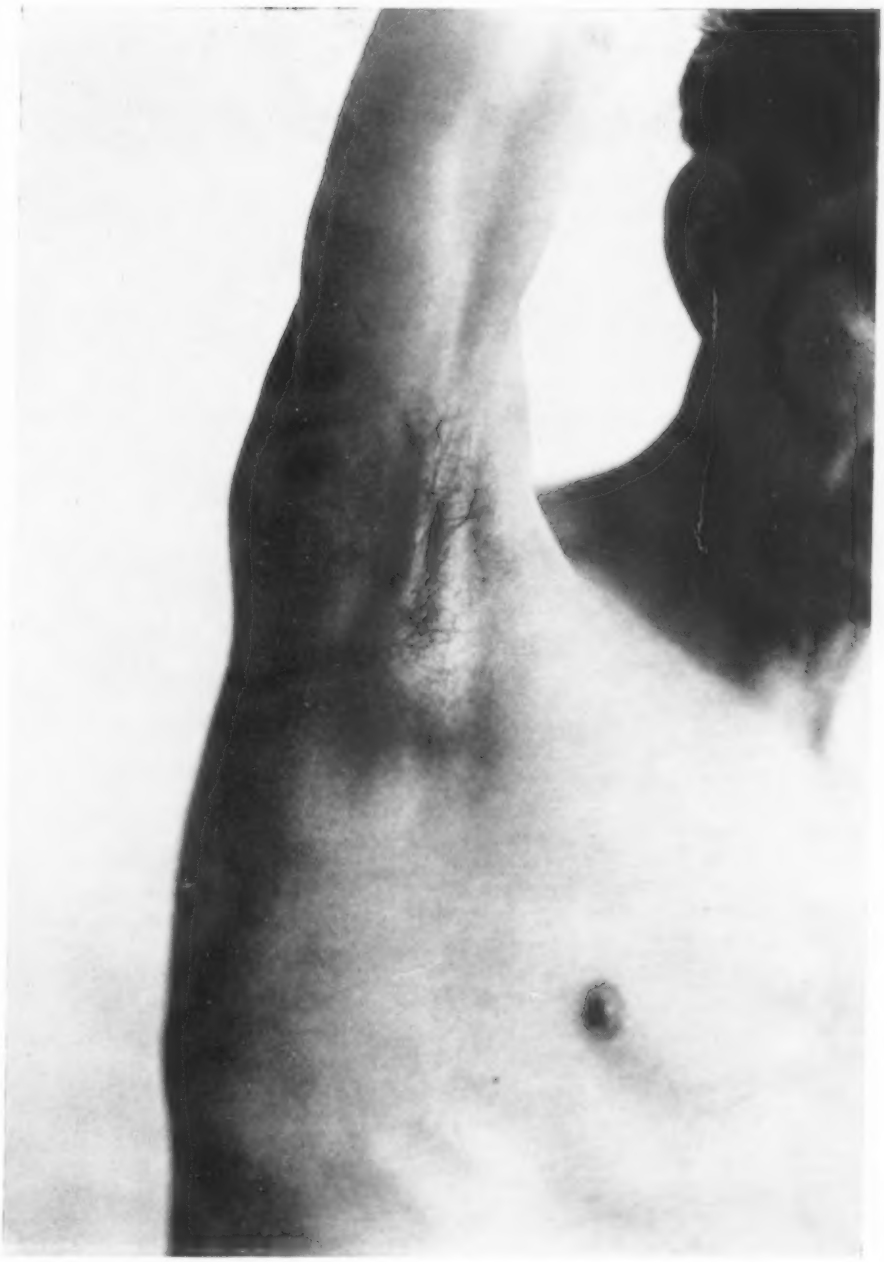

FIG. 12. Mr. J. S., case XV. Righ axillary adenopathy. Similar mass in left axilla. Six weeks after onset.

sharply punched-out ulcer, ¼ inch in diameter. From the third to the seventh day of his illness he was delirious. He described the onset of his illness, "as though I was coming down with flu." His sister who was visiting at his home, and who had learned of this disease in Kansas last year, told the doctor who was called that her brother had "rabbit disease." The doctor questioned her diagnosis. Ten days after the ulcer developed it was surgically incised. The patient felt much worse for three days following the incision. He remained in bed until the Wednesday after Thanksgiving. He then got up, feeling very weak, but was forced to return to bed for two weeks more, after which he loafed around the house for three weeks and then returned to his work feeling quite lifeless. When examined by the writer on January 20, an orange sized fluctuating axillary mass, covered by thin skin, was found, together with a diffuse radiating lymphangitis extending beyond the anterior and posterior axillary folds. Spontaneous rupture occurred two days later. The ulcer on the hand was almost completely healed but there was still a distinct excavation at the point of inoculation (see photographs). When Mr. M. was informed as to the nature of the infection he insisted that his mother must have had the disease one year previous when she assisted him in the dressing of several hundred rabbits which he had purchased in Kentucky. Mrs. M.'s history will appear under "Cases Prior to 1927."

Francis found that Mr. M.'s serum agglutinated *Bacterium tularense* completely at 1:640 and partially at 1:1280, in a specimen taken on January 20. At the Ohio Department of Health Laboratories, Berry found agglutination in a dilution of 1:640.

Case XVII

Mr. A. W. E., age 65, father-in-law of Mr. J. S. (case No. XV); farmer. Mr. E., while assisting Mr. J. S. in dressing the 500 rabbits which he had obtained in Kentucky, on the Tuesday before Thanksgiving (November 22, 1927), punctured the tip of the ring finger of the right hand, near the nail bed, with the sharp edge of a fragment of rabbit bone. On Saturday afternoon, November 26, the finger ached, and he felt very sick and was forced to take to his bed for two days. During the two days in bed he had chills and fever and at times was delirious. He then went to see a doctor who lanced the finger several times. No pus was ever evacuated as a result of the repeated incisions. On November 26, he noticed painful sensations in the right axilla. These gradually assumed the size of a lemon. The nailbed became blackened. Mr. E. felt very sick for six weeks but when questioned by the writer on January 11 stated that he felt entirely well. When examined on January 11, the scar of the ulcer on the tip of the fourth right finger was still present together with the blackened finger nail and in the axilla was a lemon sized fluctuating mass. The skin overlying the axillary mass showed marked pyodermia (see photographs).

Francis found that Mr. E.'s serum agglutinated *Bacterium tularense* in all dilutions up to 1:1280. Similar results were obtained in the Ohio Department of Health Laboratories by Berry.

Case XVIII

Mr. F. C., a negro farmer, age 40, helped Mr. S. (case No. XV) dress the 500 Kentucky rabbits on the Tuesday before Thanksgiving, 1927, and on the Saturday afternoon following Thanksgiving developed a high fever, severe backache, pains in the extremities, chills and fever, and declares that he was delirious for one week. While dressing the rabbits he stuck a sliver of rabbit bone into the fourth finger of the right hand on the medial aspect of the middle phalanx (see photograph). The resulting perforating wound refused to heal. On the Saturday after Thanksgiving, he noticed for the first time a cherry-sized lump just above the medial condyle of the right humerus. This rapidly assumed the size of an orange. *At no time did he have any palpable axillary adenopathy* (see photograph). He remained in bed for four weeks. When examined by the writer on February

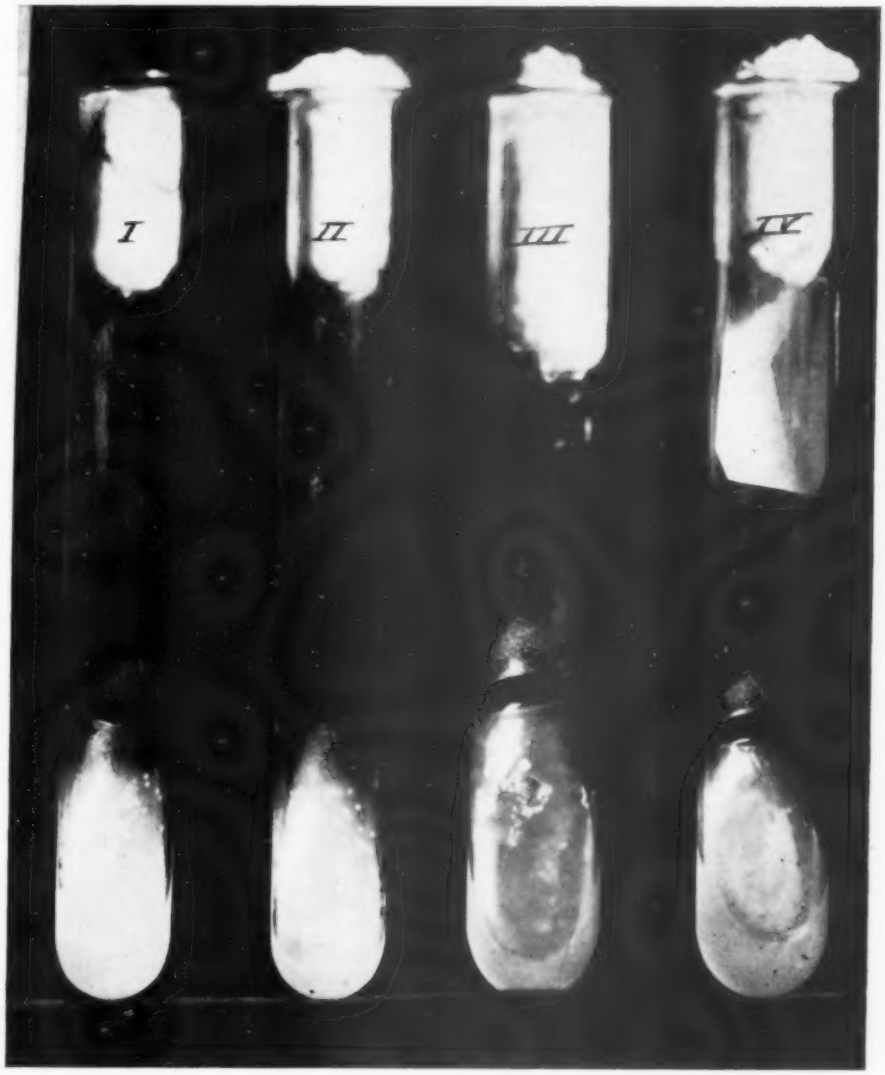

FIG. 13. Tubes 1 and 2 show colonies of *Bacterium tularense* resulting from direct inoculation from axillary tissue of Mr. J. S., case XV. Tubes 3 and 4 show growth obtained from axillary tissue of Mr. H. C., case XIX. Note fragment of abscess wall on media in tube 3, with typical colonies radiating from it.

2, 1928, the large epitrochlear mass was still present, together with the scar of the primary lesion. When questioned regarding the present state of his health Mr. E. replied that he was still very sick and unable to do his customary amount of work.

Serum from F. C. was found by Francis to agglutinate *Bacterium tularense* in all dilutions to 1:640. The serum likewise agglutinated *Bacterium abortum* (1:80) and *Bacterium melitense* (1:80).

Case XIX

Mr. H. C., age 20; dresser of rabbits for the E. F. market. On Monday, November 21, 1927, while dressing rabbits which had been received from Maysville, Kentucky, he accidentally cut the dorsal surface of the index finger of his right hand. The cut refused to heal. On Friday, November 25, there developed over the inner aspect of the right arm, overlying the medial aspect of the belly of the biceps brachii, three reddish and extremely painful nodules, the upper two of which assumed cherry size while the lowermost one assumed English walnut size (see photograph). The appearance of this nodular lymphangitis was not unlike sporotrichosis. At the same time he noticed painful swelling of the right axillary nodes. He was unable to get out of bed on this day, because of severe pains in the back and limbs and a very severe headache. A physician was called who incised the finger lesion. No actual pus escaped and the patient felt much worse following the incision. Two days later a nodule developed over the metacarpo-phalangeal articulation of the right index finger, one-half inch above the primary lesion. This too was incised by his physician. The primary lesion became larger; the center became necrotic and sloughed out, leaving an irregular deep ulcer about 3x1 cm. (see photograph). The patient's fever mounted to 105°F.; he suffered from three to five severe chills each day for five days, each chill followed by a drenching sweat. For four days he was delirious and his life was despaired of. He was severely ill for two weeks during which time he remained constantly in bed. At the end of this time he felt somewhat better and tried to get up but was unable to walk because of weakness. During the next month he spent a part of each day walking about the house but was forced to lie down from time to time because of weakness. He was still too weak to work when last examined (March 1, 1928).

On January 17, 1928, Mr. C. was admitted to the Miami Valley hospital for excision of the axillary mass and for drainage of the nodules overlying the mesial aspect of the biceps. The axillary mass was removed intact by Dr. E. R. Arn. Three guinea pigs were inoculated at once with the material from the axillary nodes and several tubes containing our human serum modification of Francis' medium were inoculated directly with the purulent fluid and with granulomatous tissue from the abscess walls. Three days later the first growth was noticed. In one of the tubes in which a pea-sized fragment of tissue from the abscess wall had been placed small spherical whitish colonies were seen to radiate from the tissue. (See photograph.) Growth was obtained on five of the six tubes inoculated. To prove that the organism was *Bacterium tularense* the same procedure was carried out as in the J. S. case (case No. XV) and every requirement for the identity of the organism was satisfied.

Microscopic examination of the tissue from the axilla showed large areas of caseation necrosis, with well defined fibroblastic and epithelioid granulation tissue at the periphery. There were large Langans' foreign-body giant cells in the epithelioid granulation tissue. There was no angioblastic proliferation in the granulation tissue.

The serum of Mr. H. C., collected on January 14, was found by Francis to agglutinate *Bacterium tularense* in all dilutions up to 1:1280. At the Ohio State Health Laboratories, Berry obtained the same results.

Case XX

Mr. C. J. P., age 25, dressed rabbits at the E. F. market. He cut the skin of his right thumb, over the middle of the proximal phalanx, with a rabbit bone, on November 17, 1927. The wound in the thumb re-

fused to heal. Four days after the initial injury, an English walnut size mass appeared in the right axilla. He felt quite ill, but did not quit work even though he was unable to use the right hand and arm. He had a severe headache and backache but does not think that he had a high fever. He feels perfectly well now. There is still present in the right axilla a firm English walnut sized mass showing no tendency to suppurate. Serum was not obtained until February 17, just three months after the inoculation of his thumb. It was found by Francis to agglutinate *Bacterium tularense* in all dilutions to 1:320.

Case XXI

Mr. A. L. G., age 34, dressed rabbits at an Atlantic and Pacific Tea Company's store in Dayton, on November 18, 1927. These rabbits had been received from the J. O. F. market, which means that they were Maysville, Kentucky, rabbits. While dressing the rabbits, he stuck the sharp edge of a meat hook under the finger nail of the middle finger of the right hand. His finger became somewhat swollen and began to discharge serous material within twenty-four hours. Two days after the injury to his finger, he experienced a very severe chill, followed by a drenching sweat. His fever became

FIG. 14. Mr. C. D. M., case XVI. Healing ulcer in web between right thumb and index finger, eight weeks after onset.

very high; he had repeated chills and sweats for ten days, accompanied by severe body aches and headache. On the day following the first severe chill he noticed a painful mass in the right axilla, to which flax seed poultices were applied for three days. At first there were two hickory nut sized masses, which later became confluent and formed a lemon-sized mass (see photograph). Because of economic difficulties he felt forced to work through the period of his illness but returned to his home every night completely exhausted.

On February 20, 1928, Mr. G. was admitted to the Miami Valley hospital, where the axillary mass was removed intact by Dr. E. R. Arn. All attempts to recover the organism by animal passage and by the inoculation of culture media, were unsuccessful. Serum collected on February 7 was found by Francis to agglutinate *Bacterium tularense* in all dilutions to 1:1280.

Microscopic examination of axillary tissue sections showed large areas of caseation necrosis, surrounded by a broad zone of avascular fibroblastic and epithelioid granulation tissue, containing occasional Langhans' giant cells. There was endothelial proliferation, with partial obliteration of the venules and arterioles.

Case XXII

Mr. E. A. M., a patient of Drs. W. and C. J. Ryan and Dr. Joseph O. Porter, age 67, a retired farmer, killed several rabbits in the woods three miles northeast of Eaton, Ohio, on November 16, 1927. He dressed the rabbits in the field. The patient remembers distinctly that the livers were dotted with small whitish spots. On November 18 he noticed a small papule on the dorsal surface of the web between the thumb and index finger of the left hand. Several hours later he noticed another papule on the same hand on the lateral surface of the ring finger overlying the distal interphalangeal articulation. These gave practically no pain. On the afternoon of November 18, the patient began to feel drowsy and depressed. In the evening he had a chill. The next morning he felt rather weak but thought he might wear it off by hunting. He went out for a short time but felt forced to return and go to bed. The following morning the arm was markedly swollen and very painful. He had a high fever, and a rapid pulse, with repeated chills and sweats. His wife states that he was "out of his head" part of the time. In the evening a painful swelling developed in the left axilla and there were distinct reddish-blue streaks in the skin of the inner aspect of the arm. Several painful nodules developed along these streaks. The mass over the arm finally reached the size of a hen's egg.

When seen upon December 6, the patient was very anemic, toxic, and had lost considerable weight. He was highly nervous, irritable, and greatly depressed. He was convinced that he could not live. The primary lesion on his left hand was covered by a crust. When this was removed there remained a deep, sharply punched-out ulcer. On January 17, the patient was again seen by his physician who found him in good spirits. He had regained ten pounds but felt weak at times. The lesion on the left hand was practically healed but the axillary mass was not greatly reduced in size.

The serum of Mr. M., taken on December 1, 1927, was found by Francis to agglutinate *Bacterium tularense* in all dilutions to 1:180.

Case XXIII

Mrs. F. A. S., age 42; housewife; patient of Dr. N. C. Hochwalt. Mrs. S. was presented with a rabbit which had been brought from Kentucky. She prepared the rabbit for cooking on the evening of November 28, 1927, and cut her thumb with a sharp fragment of rabbit bone. During the afternoon of November 30 she complained of chills, fever, and generalized aching sensations. On December 2, she complained of soreness of the palmar surface of the distal phalanx of the right thumb; the fever and aching continued. The patient was first seen by Dr. Hochwalt on the morning of December 2. Examination revealed a slight swelling of the distal phalanx of the right thumb, together with enlargement of the epitrochlear glands. There was no axillary swell-

ing. The temperature at this time was 103°F., pulse 120. The patient remained in bed for four weeks during which time the temperature varied from 99° to 103°F. The area on the thumb became ulcerated with central necrosis while the epitrochlear glands assumed the size of a robin's egg.

On February 8, 1928, the ulcerated area on the thumb was smaller but not yet healed and was still painful. The epithochlear mass had not diminished in size and was still tender. *There was no axillary involvement at any time.*

Serum of Mrs. S., taken on February 8, 1928, was found by Francis to agglutinate *Bacterium tularense* in all dilutions to 1:1640.

B. Cases Prior to 1927

Many Dayton physicians indicated to the writer that they had seen patients in previous years who had unquestionably been victims of this disease. The writer visited these individuals and in nearly every case elicited a very characteristic history. A circular letter was sent to all of the psysicians of the city asking for information regarding old possible cases of tularemia. As result of this letter six old cases were discovered, all among market men. The writer then visited each of the larger markets of the city and talked with the proprietors regarding cases of "rabbit fever." As a result of these investigations, 25 cases occurring prior to 1927 were unearthed. It was definitely established that tularemia has been present in this city for twenty years.

Case XXIV

Mr. M. T., age 55; wholesale produce dealer. During November of *1908*, while dressing rabbits, he cut his right hand with a rabbit bone, three days after which he became acutely ill and suffered from chills and sweats, high fever, prostration and enlarged right axillary lymphnodes. The rabbits were purchased from B. L. Co., of St. Louis, Missouri, and the rabbits had been killed in Missouri and Kansas.

Serum collected on February 13, 1928, 19 years and 3 months following the onset of the disease, was found to agglutinate *Bacterium tularense* in all dilutions to 1:160 (Francis).

This is the earliest case of tularemia of which there is any record east of the Mississippi river.

Case XXV

Mr. J. H. A., age 68. Just before Thanksgiving time, *1912*, he scratched his hands with rabbit bones while dressing rabbits in the F. market of Dayton. On the Sunday before Thanksgiving, 1912, he was taken suddenly ill with a high fever, chills and sweats, and great prostration. He remained in bed for one month, during which time he suffered from a severe watery diarrhea. Huge axillary masses, of orange size, developed in both axillae, together with a cherry sized mass in the right epitrochlear area. Three weeks after the onset of his illness the axillary masses were surgically drained and the drainage continued for many weeks. He was unable to return to his work until the following April. He did not feel well for over a year.

Serum of Mr. A., collected on February 15, 1928, was found by Francis to agglutinate *Bacterium tularense* in all dilutions to 1:80.

Case XXVI

Mr. J. C., age 50, dressed rabbits at the F. market during Thanksgiving week, *1913*. Three days later he experienced a severe chill, followed by sweats and a rapidly mounting fever. His doctor felt that he was acquiring "grippe." In the right axilla there developed multiple cherry sized painful swellings. No ulcer developed at any time on the right hand. Mr. C. was incapacitated for work for three weeks, and after he returned to his work felt exhausted for many weeks.

Serum of Mr. C., collected on March 14,

TABLE II
Cases Prior to 1927

Case No.	Initials	Sex	Age	Occupation	Source of Infection	Primary Lesion	Incubation Period	Onset Date	Adenopathy	Suppuration	Agglutination (by Francis)	Convalescence	Type
25	W.T.	M	55	Produce dealer	Missouri and Kansas rabbits	Right hand	3 days	Nov., 1909	Right axillary	None	1:160	Many weeks	UG
26	JHA	M	58	Market man	Kentucky and Ohio rabbits	Both hands	3-4 days	Nov., 1912	Right and left axillary, right epitrochlear	Incision	1:80	Five months	UG
27	J.C.	M	50	Market man	Kentucky and Ohio rabbits	No ulcer	Three days	Nov., 1912	Right axillary	None	1:320	Short	G
28	B.K.	M	38	Butcher	Kentucky rabbits	Left thumb	4-5 days	Nov., 1914	Right and left axillary, left epitrochlear	Incision		46 days plus	UG
29	R.T.	M	61	Market man	Kentucky rabbits	Right thumb, left hand	Two days	Nov., 1916	Right and left axillary	Incision	1:320	Several months	UG
30	B.F.	M	54	Market man	Missouri rabbits	Left middle finger	Four days	Nov., 1916	Questionable		1:320	Six months	?
31	C.F.	M	49	Market man	Kentucky rabbits	Palm, left hand	3-4 days	Nov., 1918	Left axilla	Spontaneous	1:160	6 weeks plus	UG
32	CFF	M	43	Proprietor of market	Missouri and Kansas rabbits	No ulcer	Three days	Nov.11,1918	Right and left axillary	Incision	1:80	Several weeks	G
33	E.M.	M	41	Market man	Missouri and Kansas rabbits	Left index finger	Three days	Nov.11,1918	Left axillary	Incision	1:320	Eight months	UG
34	C.F.	M	40	Market man	Missouri and Kansas rabbits	Right thumb	Six days	Nov.14,1918	Right axillary	Incision	1:20	Five months	UG
35	H.S.	M	42	Market man	Kentucky rabbits	Right index finger	Four days	Nov., 1919	Right axillary and epitrochlear	None	1:80	Four months	UG
36	W.E.	M	38	Merchant	Local rabbits	Right hand	1-2 days	Nov., 1920	Right axillary	None	1:40	One month	UG
37	W.H.	M	60	Market man	Kentucky rabbits	Left middle finger	Three days	Nov., 1922	Right and left axillary	Incision spontaneous	1:160	Three months plus	UG
38	P.H.	M	46	Butcher	Kentucky rabbits	Right index finger	Two days	Nov., 1922	Right axillary	None	1:160	One year	UG
39	T.A.	M	45	Butcher	Kentucky rabbits	None	Five days	Nov., 1922	Left axillary	Excised	1:40	Six months	G
40	W.F.	M	38	Market man	Kentucky rabbits	Left ring finger	Two days	Nov.13,1922	Left axillary and epitrochlear	Incised	1:80	Four months	UG
41	J.H.	M	47	Market man	Missouri rabbits	Right middle finger	Four days	Nov.19,1923	Right axillary	Incised	1:320	10 weeks plus	UG
42	M.H.	F	55	Rabbit dresser	Kentucky rabbits	None	Unknown	Nov., 1923	Right axillary and epitrochlear	None	1:80	Several months	UG
43	V.H.	F	48	Rabbit dresser	Kentucky rabbits	None	Unknown	Nov., 1923	Right axillary and epitrochlear	Incision	1:80	Four months	G
44	O.J.	M	30	Market man	Kentucky rabbits	Left fifth finger	Seven days	Nov., 1924	Left axilla	Incision	1:160	Several months	UG
45	DeR	F	38	Rabbit dresser	Kentucky rabbits	Left thumb	Four days	Nov., 1924	Left epitrochlear and axillary; nodular lymphangitis	Incision and spontaneous	1:80	Five months	UG
46	JHK	M	54	Market man	Kentucky rabbits	Right thumb	Four days	Nov., 1926	Right axillary	Incision	1:160	8months plus	UG
47	JHS	M	36	Butcher	Kentucky rabbits	Between right middle and ring finger	One day	Nov.26,1926	Right axillary and epitrochlear	Incision	1:160; partial 1:320	Several weeks	UG
48	C.R.	M	39	Butcher	Kentucky rabbits	Left little finger	Five days	Nov.21,1926	Left and right axillary; left and right epitrochlear	Incision	1:80	Six months	UG
49	M.M.	F	56	Housewife	Kentucky rabbits	Right fourth finger	Two days	Nov., 1926	Right axillary	None	1:320	Several months	UG

G = Glandular type UG = Ulceroglandular type

1928, was found by Francis to agglutinate *Bacterium tularense* in all dilutions to 1:320.

Case XXVII

Mr. B. K., age 38, dressed rabbits at the A. market at Thanksgiving time, *1914*. He scratched the left thumb with either a knife or a sharp rabbit bone. Four days later he developed a fever of 104°F. with chills, sweats, severe backache and headache. He remained in bed for 16 days. Lemon sized painful axillary swellings developed on both sides. In the left epitrochlear region a lemon size painful swelling developed. All 3 of the masses were surgically drained by Dr. A. H. Dunham. Mr. K. was unable to return to his work for 46 days after the onset.

Case XXVIII

Mr. R. T., age 51, dressed Kentucky rabbits at the F. market during the four days before Thanksgiving of *1916*. He stuck sharp fragments of rabbit bones into the tip of the right thumb, into the thenar eminence of the left hand and into the palmar surface of the web between the thumb and index finger of the left hand. Two days later he had a severe chill and severe aching sensations in the back and extremities. He states, "I thought the flu was coming over me." He took to his bed, where he remained for two weeks. Two days after taking to his bed, he noticed painful swellings in both axillae. The mass in the right axilla assumed the size of an orange, while that in the left axilla became of hen's egg size. Two weeks after the onset of his illness the mass in the right axilla was drained surgically. The patient lost 20 pounds during the first two weeks of his illness. In view of the fact that he weighed 108 pounds prior to his illness, this represents a considerable loss. He did not regain his strength for over one year.

Serum of Mr. T., collected on February 25, 1928, was found by Francis to agglutinate *Bacterium tularense* in all dilutions to 1:320.

Case XXIX

Mr. B. F., age 64, dressed rabbits which had been received from St. Louis at the F. market during Thanksgiving week, *1916*. He stuck the sharp point of a fragment of rabbit bone into the palmar surface of the skin of the left middle finger overlying the proximal phalanx. Four days later the hand became greatly swollen, reddish-blue streaks ascended the arm and he felt very weak. His powers of recall are poor and he does not remember whether there were any epitrochlear or axillary swellings. He was out of work for six months. The finger was incised surgically many times with a resulting permanent ankylosis of both interphalangeal articulations.

Serum of Mr. F. collected on February 25, 1928, was found by Francis to agglutinate *Bacterium tularense* in all dilutions to 1:320.

Case XXX

Mr. O. F., age 49, dressed rabbits at the F. market, Dayton, during the month of November, *1918*. On the day after Thanksgiving, 1918, he was taken suddenly ill with a disease which was diagnosed "grippe." Just before Thanksgiving day he had stuck the sharp edge of a turkey bone into the palm of the left hand. At the same time that he was taken ill, a mass appeared in the left axilla and assumed the size of a hen's egg. This mass drained spontaneously after about one month and caused him great pain until the following February. The axillary drainage continued for five weeks. For economic reasons he did not go to bed during his entire illness, although he admits that he was much too sick to work.

Serum of Mr. F., collected on February, 1928, was found by Francis to agglutinate *Bacterium tularense* in all dilutions to 1:160.

Case XXXI

Mr. O. F. F., age 43, proprietor of F. market, Dayton, dressed rabbits which had been received from B. L. company, St. Louis, on November 8, *1918*. The rabbits had been killed in Missouri and Kansas. On Armistice day (November 11, 1918) he was taken suddenly ill and was forced to take to his bed. While dressing rabbits he had scratched both hands in many places but does not remember any papules or ulcers on either

hand. On the day on which he was taken sick he noticed lemon sized, excruciatingly painful masses in both axillae. He remained in bed for one week, during which time he suffered from chills and sweats and a moderately high fever. The axillary masses were drained surgically within a few days of the onset of his illness. The drainage continued for three weeks. He returned to his work at the end of one week, still feeling quite ill.

Serum of Mr. F. collected on February 25, 1928, was found by Dr. Francis to agglutinate *Bacterium tularense* in all dilutions to 1:80.

FIG. 15. Mr. C. D. M., case XVI. Axillary adenopathy. Spontaneous rupture occurred two days after photograph was taken, eight weeks after onset.

Case XXXII

Mr. E. M., age 41, dressed rabbits witn O. F. F. (case XXXI). On Armistice Day, *1918*, a reddish papule developed on the medial aspect of the distal phalanx of the left index finger. He does not remember cutting or scratching his hands while dressing the rabbits. While walking on the street on Armistice day, he fainted. He was confined to his bed for 17 days with a fever which remained around 104°F. The center of the papule on the finger became necrotic and sloughed out after one week. He did not notice any mass in the left axilla until 18 days after the onset of his illness. He

was unable to do any work for one month. He was then able to work from three to four hours a day until the next July when he did a full day's work for the first time. The primary lesion and the axillary mass were surgically incised, the latter on December 31, 1918. The drainage continued until July, 1919. He felt very weak until the following September. He is now in excellent health.

Serum of Mr. M., collected on February 25, 1928, was found by Francis to agglutinate *Bacterium tularense* in all dilutions to 1:320.

Case XXXIII

Mr. C. F., age 40, likewise assisted Mr. O. F. F. (case XXXI) in the dressing of the St. Louis rabbits. He cut the right thumb on a rabbit bone on November 8, *1918*. The cut refused to heal. Six days following the injury he was forced to take to his bed because of high fever and chills. He was delirious for five days. He has no recollection as to what occurred during that period. After he had been in bed for one week the right axillary glands became large and painful. These were incised and continued to drain for three months. He did not return to his work for 5 weeks. He tired very easily and was unable to do the amount of work to which he was accustomed for five months, after which time he slowly improved.

Serum of Mr. F. collected on February 25, 1928, was found by Francis to agglutinate *Bacterium tularense* in all dilutions to 1:20.

Case XXXIV

Mr. H. S., age 42, dressed rabbits which had been received from Louisville, Kentucky, at the F. market just prior to Thanksgiving, *1919*. He scratched the right index finger with a sharp rabbit bone. Four days later he developed what he considered to be "grippe." A doctor was called who pronounced it "blood poisoning." He suffered from chills, high fever, severe headache and body aches for two weeks. He states that he was very weak for four months. The right axillary and epitrochlear glands were greatly swollen when he took to his bed. He was unable to return to his work for five months. The axillary glands were not incised nor did they rupture through the skin.

Serum of Mr. S. collected on February 25, 1928, was found by Francis to agglutinate *Bacterium tularense* in all dilutions to 1:80.

Case XXXV

Mr. W. E., age 38, patient of Dr. A. B. Brower, injured the back of the right hand while dressing rabbits during Thanksgiving week, *1920*. From 24 to 48 hours after the initial injury painful right axillary swelling occurred, accompanied by fever and chills. He did not go to bed, but was unable to use the hand and arm for one month. He did not do any work during that time.

Serum of Mr. E., collected on February 24, 1928, was found by Francis to agglutinate *Bacterium tularense* in all dilutions to 1:40.

Case XXXVI

Mr. W. H., age 60, dressed rabbits at the F. market during Thanksgiving week of *1922*. He cut the tip of the middle finger of the left hand with a rabbit bone. Three days after this injury a painful mass appeared in the left axilla which gradually assumed the size of a grape fruit. A similar mass, which reached orange size, appeared in the right armpit. A small deep ulcer developed at the site of the injury to his finger. Simultaneously with the development of the axillary masses he experienced repeated chills and sweats, an exceedingly high fever, and was delirious for two weeks. He was strictly confined to bed for 12 weeks. The mass in the left axilla was drained surgically two weeks after the onset of his illness. The mass in the right axilla drained spontaneously about one month after the onset of his illness. Mr. H. was unable to return to his work for three months. He did not regain his former strength, and was was unable to completely elevate either arm for over one year.

Serum of Mr. H. collected on February 15, 1928, was found by Francis to agglutinate *Bacterium tularense* in all dilutions to 1:160.

Case XXXVII

Mr. P. H., a market man, age 46, scratched the right index finger, medial aspect of the distal phalanx, while dressing rabbits on the Tuesday before Thanksgiving, *1922*. These rabbits had been brought to Dayton from Maysville, Kentucky. On Thanksgiving forenoon, he felt that he was "coming down with grippe" and with "rheumatic pains" in the right shoulder. The next morning he came to work at 9 o'clock. Just after arriving at his market, "everything went black and I had a real chill." He went home and went to bed. In the afternoon he noticed a mass of hen's egg size in the right axilla. He could not remain in bed because of shooting, pounding pains in his head. The finger lesion was Dakinized repeatedly. It was treated by his doctor daily for 49 days. The axillary mass was not incised nor did it break through the skin. He dragged himself around for one year feeling as though he had lost his strength. He is now a huge, muscular individual.

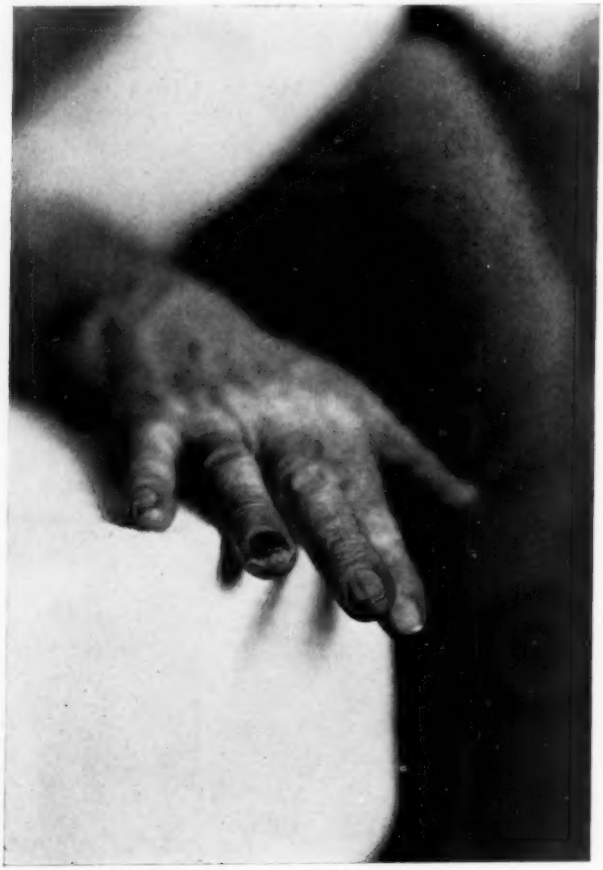

FIG. 16. Mr. A. W. E., case XVII. Healing ulcer of tip of right ring finger, with necrotic nail. Six weeks after onset.

Serum of Mr. H., collected on February 17, 1928, was found by Francis to agglutinate *Bacterium tularense* in all dilutions to 1:160.

Case XXXVIII

Mr. I. A., age 45, assisted Mr. P. H. (case XXXVII) in dressing the Maysville, Kentucky, rabbits on the Tuesday before Thanksgiving, *1922*. Mr. A. is convinced that there was no scratch or cut on his hand or fingers as a result of any injury acquired while dressing rabbits. On the Sunday after Thanksgiving his left arm became very sore, with excruciating pain radiating from the left axilla. On the next day he developed a high fever, but felt forced to go to work. On Tuesday, he had to quit work and take to his bed. He noticed for the first time on this day a left axillary swelling, which assumed lemon size. On the following Sunday he developed chills and sweats and his fever increased and he was delirious for many days. His condition was diagnosed pneumonia. He remained in bed until the day after Christmas of 1922. He went to work on the first of March, 1923, but after two weeks was forced to quit because of the painful axillary mass. This mass was excised on March 15. He was unable to return to his work until the first of May. During his illness he lost 12 pounds.

Serum of Mr. A. taken on February 15, 1928, was found by Francis to agglutinate *Bacterium tularense* in dilutions to 1:40.

Case XXXIX

Mr. W. F., age 38, acquired the disease while dressing rabbits at the F. market, on November 11, *1922*. On November 13, 1922, the left axillary glands became enlarged to lemon size. Several of the left epitrochlear glands reached cherry size. A small papule appeared at the same time on the left ring finger, which soon became ulcerated, leaving a dime size deep depression. The first symptom was a severe chill followed by a drenching sweat and high fever. He states that he felt that he was "coming down with grippe." The primary lesion was not incised but the axillary glands were surgically drained by Dr. R. R. Shank. Mr. F. was unable to return to his work because of extreme weakness until March 1, 1923. When examined on February 27, 1928, a hazelnut sized firm epitrochlear gland still remained.

Serum of Mr. F., collected on February 28, 1928, was found by Francis to agglutinate *Bacterium tularense* in all dilutions to 1:80.

Case XL

Mr. J. H., age 47, dressed rabbits which had been shipped to Dayton, from St. Louis, Missouri, on November 15, *1923*. He stuck the sharp edge of a broken rabbit bone into the palmar surface of the middle finger of the right hand overlying the metacarpophalangeal articulation. He immediately put turpentine on the finger lesion. It is an old belief among market men that turpentine is the best remedy to use in order to avoid "rabbit fever." The finger lesion refused to heal. Four days later, bluish-red streaks appeared over the flexor surface of the forearm, and he experienced a severe chill, followed by a fever which went to 105°; he was delirious for four days and suffered from a severe headache and back pains. Two days after the onset of his illness his doctor noticed a mass in the right axilla. He remained in bed for seven days, after which he got up, against his doctor's orders, in order that he might go to his home in Columbus. Immediately upon arriving home he went to bed for two weeks more. He tried to "bring the mass in the armpit to a head" with poultices, but the mass seemed to become larger and reached the size of a hen's egg. It was surgically drained three weeks after the onset of his illness. It continued to drain for seven weeks. He was out of work for ten weeks and when he returned to work felt very weak for three months. He lost 40 pounds during his ten weeks' illness.

Serum of Mr. H., collected on February 20, 1928, was found by Francis to agglutinate *Bacterium tularense* in all dilutions to 1:320.

Case XLI

Mrs. M. H., age 55, the mother of H. H. (case V), dressed rabbits at the C. market during the week before Thanksgiving, *1923*. She does not remember any primary lesion on her hand and is quite certain that she acquired no scratches or cuts while dressing the rabbits. On Thanksgiving, 1923, she

suffered from chills and fever, but did not feel that she could go to bed because of pressing duties. She noticed painful swellings in the right axilla and epitrochlear glands, the former reaching lemon size. The epitrochlear and axillary masses never drained spontaneously, nor were they surgically incised. She felt very weak until during the spring and summer of 1924 and was unable to return to her work until the fall.

Serum of Mrs. M. H., collected on February 25, 1928, was found by Francis to agglutinate *Bacterium tularense* in all dilutions to 1:80.

Case XLII

Mrs. W. H., age 48, assisted Mrs. M. H. (Case XLI) in dressing rabbits at the C. market. A third woman (Mrs. C. H.) who helped dress these rabbits was taken acutely ill at the same time as Mrs. M. H. and Mrs. W. H., and after two weeks of identical illness, died. Mrs. W. H. does not remember any scratch or cut on her hands. The day before Thanksgiving, 1923, she felt that she was "coming down with grippe," because of a severe headache and aching sensations in the back and extremities. She noticed on that day a papule on the tip of the middle finger of the right hand as well as epi-

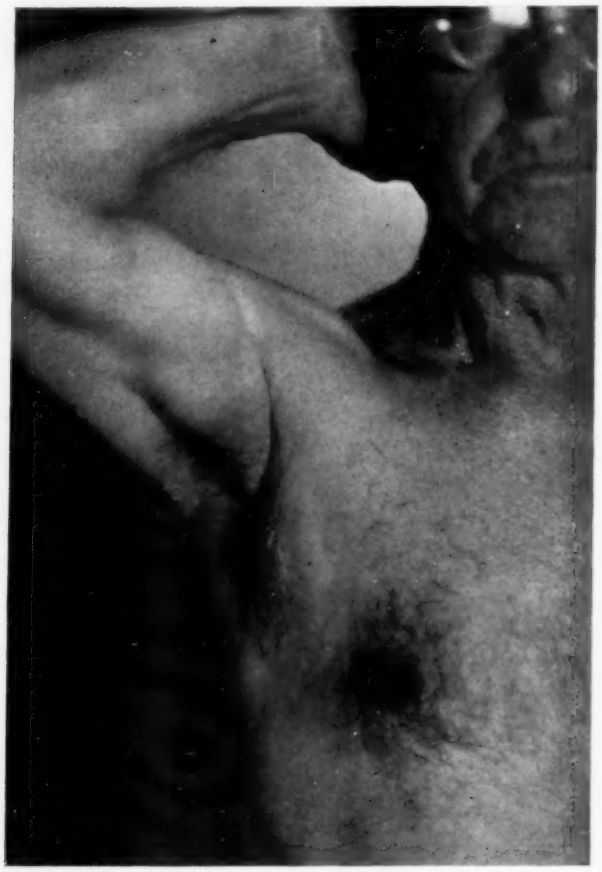

FIG. 17. Mr. A. W. E., case XVII. Axillary adenopathy, with diffuse pyodermia. Six weeks after onset.

trochlear adenitis which soon reached lemon size, and an English walnut size mass in the right axilla. She suffered from high fever, transient delirium, chills and sweats for ten days. She lost an indeterminate amount of body weight. The axillary mass was surgically drained the day before Christmas, 1923. She was unable to do any work until the following March. She states that she has never been entirely well since this illness.

Serum of Mrs. W. H., collected on March 1, 1928, was found by Francis to agglutinate *Bacterium tularense* in all dilutions to 1:80.

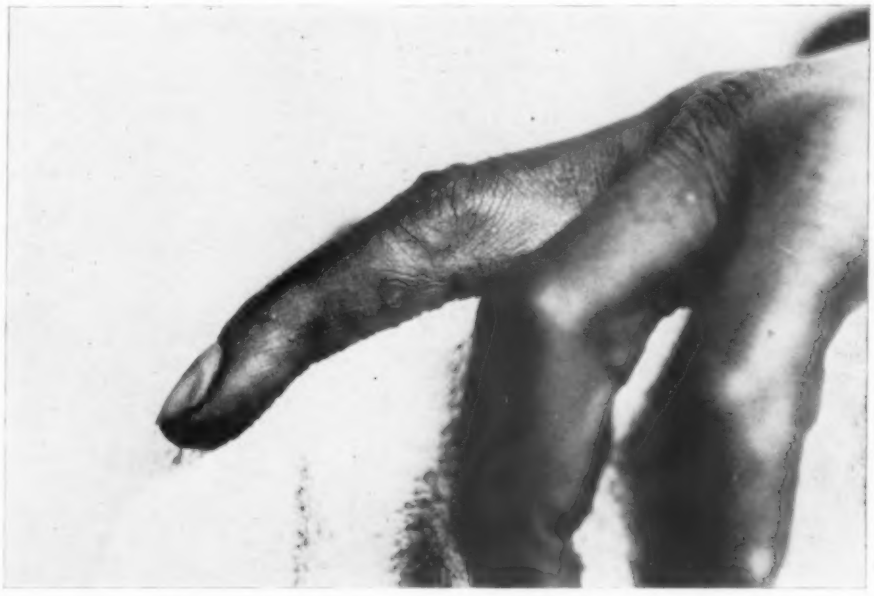

FIG. 18. Mr. F. C., case XVIII. Healing ulcer of fourth finger of right hand. Nine weeks after onset.

Case XLIII

Mr. O. J., age 30, dressed rabbits at the E. F. market, just before Thanksgiving, *1924*. He cut the little finger of the left hand, just above the nail, with a sharp rabbit bone. One week later, four masses appeared in the left axilla, each of walnut size. He suffered from high fever, chills and sweats. The lesions of the hand and axilla took three months to heal. Dr. O. C. Henderson drained the axillary masses surgically about two weeks after they first appeared. Dr. Henderson told him at that time that he had the disease known to market men as "rabbit fever." Even though he worked through his period of illness, he felt very weak for several months. He has been in good health ever since.

Serum of Mr. J. collected on February 13, 1928, was found by Francis to completely agglutinate *Bacterium tularense* in a dilution of 1:80 and to partially agglutinate the organism at 1:160.

Case XLIV

Mrs. G. DeB., age 38, helped clean and dress rabbits at the C. market on the Saturday before Thanksgiving, *1924*. She scratched the left thumb with a sharp fragment of rabbit bone. On the following Wednesday she became acutely ill with "grippe-like" symptoms. A lemon size mass developed in the left epitrochlear region and an orange size mass in the left axilla. Just above the bend of the left elbow a walnut size nodule developed. She applied poul-

tices to the epitrochlear mass and on the week before Easter, 1925, it drained spontaneously. One week after the epitrochlear drainage the axillary mass was surgically incised and about one-half pint of thick yellowish material escaped. During these five months Mrs. DeB. was unable to do her usual amount of work and it was only after the abscesses were drained that she began to feel better.

Serum of Mrs. DeB., collected on March 13, 1928, was found by Francis to agglutinate *Bacterium tularense* in all dilutions to 1:80.

Case XLV

Mr. J. H. K., age 54, cut his right thumb accidentally with a knife while dressing rabbits on the eighth day of November, *1925*, at the F. market, of Dayton. Four days after the injury, he complained of pain in the thumb, became very weak, developed a high fever, with chills and sweats and body aches. The ulcer which developed was incised and cauterized two days later. Four days after the pain developed in the thumb he complained of painful swellings in the right axilla. These rapidly fused and assumed grapefruit size. Two weeks later, when fluctuation developed, the glands were incised and drained by Dr. Damon Crist. The material which escaped on the initial drainage was thin and watery, but rapidly became very thick. During the first few weeks of his illness he lost considerable weight. The ulcer continued to give considerable pain and it was several months before it was completely healed. The axillary drainage continued for several weeks. He was unable to elevate his arm for many months. Mr. K. did not return to his work until May of 1926. The patient states that he has never felt well since the onset of his illness. Examination by the writer on January 27, 1928, showed an atrophic depressed scar of the ulcer 6 m.m. in diameter. In the right axilla was an atrophic linear scar healed by first intention, 3 cm. in length; there was no palpable axillary lymphadenopathy.

Serum of Mr. K. collected on January 27, 1928, agglutinated *Bacterium tularense* in all dilutions to 1:160 (Francis).

Case XLVI

Mr. J. G. S., age 36; butcher. While dressing rabbits on November 25, *1926*, he accidentally cut his hand with a rabbit bone. On the next day his arm became painful and a tender swelling developed in the axilla. He developed a high fever with repeated chills and sweats and remained in bed for one week. He was not seen by a physician until one week after the onset of his illness, when he was found to have a temperature of 101.8°F. There was found a small abrasion on the dorsal surface between the middle finger and the ring finger of the right hand. It had an indurated border with a small central deep ulcer, with a necrotic base. The right axillary lymphnodes were swollen to the size of a hen's egg. The right epitrochlear lymphnodes were of cherry size and very painful. At this time he had 12,800 white blood cells per cm. with 60 per cent polymorphonuclear neutrophiles, 35 per cent small lymphocytes and 5 per cent large lymphocytes. The axillary mass became fluctuant and was surgically drained. Smears were negative for tubercle bacilli.

Mr. S. S., age 50, a brother of Mr. J. G. S., likewise a butcher, dressed rabbits at the same time. He cut the right index finger, with a rabbit bone, on November 20, *1926*. The finger lesion did not heal. Five days later an ascending nodular lymphangitis developed together with axillary and epitrochlear lymphadenitis. He developed high fever, repeated chills and sweats, was greatly prostrated and lost considerable weight. His fever persisted until the day of his death, December 15, 1926. His death certificate was signed, "rabbit bone infection," by Dr. R. D. Potts.

Serum of Mr. J. G. S. collected on January 20, 1928, was found by Francis to agglutinate *Bacterium tularense* completely in all dilutions to 1:160 and partially in 1:320 dilution. Similar results were obtained by Berry, at the Ohio Department of Health Laboratories.

Case XLVII

Mr. C. R. age 39; butcher. On the 16th of November, *1926*, while cleaning rabbits at the O'B. market, Mr. R. cut the little finger of the left hand over the proximal interphalangeal articulation with a rabbit bone. He put iodin on the cut immediately. Five days later the finger gave him considerable pain in the morning. In the afternoon, he noticed a painful swelling at the left elbow. During the next 4 hours he developed a fever of 103.6°F. Because of financial difficulties, he remained at work even though he suffered from severe chills and sweats, splitting headache and severe body aches. The next day after the mass appeared at the left elbow he noticed a painful swelling in the left axilla. The axillary mass assumed walnut size, while the mass in the anticubital fossa reached orange size. Four days after the onset of his illness he noticed a mass in the right axilla which reached orange size in three days. The day following the appearance of the right axillary mass a similar swelling appeared in the right anticubital fossa, which reached orange size. The mass in the right axilla and right anticubital fossa were incised ten times and drainage continued for six months. During this six months's period he felt very

FIG. 19. Mr. F. C., case XVIII. Epitrochlear adenopathy. No axillary adenopathy. Nine weeks after onset.

weak, was forced to lie down immediately after finishing his work, and did not commence to regain his lost weight until the following April. He is now (February 7, 1928) in excellent health.

Serum of Mr. R., collected on February 7, 1928, was found by Francis to agglutinate *Bacterium tularense* in all dilutions to 1:80.

Case XLVIII

Mrs. M. M., age 66; housewife. It was on Mrs. M.'s farm that J.S., C.D.M., A.W. E., and F. C. (cases XV to XIX) dressed the 500 rabbits purchased in Kentucky, just before Thanksgiving of this year. For many years she has assisted her son, C.D.M., in dressing rabbits which he has brought from Kentucky. On the night before Thanksgiving, *1926*, while helping C.D.M. dress rabbits she cut the fourth finger of the right hand with a sharp rabbit bone fragment. In two days she became very sick and called in a physician who pronounced it "old-time bone-breaking grippe." An ulcer remained on the finger at the site of the inoculation for many weeks and a large right axillary mass appeared. On the day after Thanksgiving she developed a high fever, chills and sweats, severe headache, transient periods of delirium, and severe body aches. She was forced to remain in bed for seven weeks. She would try to get up and would discover that she was too weak, and would return to her bed. She claims that she has never felt well since this illness. A small deep scar of the ulcer still remians.

Serum of Mrs. M. M., collected on February 2, 1928, was found by Francis to agglutinate *Bacterium tularense* in all dilutions to 1:320.

Summary and Conclusions

1. The discovery of forty-nine cases of tularemia in Dayton, Ohio, in the short period of four months, leads to the inevitable conclusion that tularemia is a common disease.

2. The most rapidly fatal case of tularemia of which there is any record (4 days, 7 hours) provided an opportunity to study the early gross and histopathological lesions.

3. Twenty-four cases occurred during November, 1927, and in all but five instances were due to contact with Kentucky rabbits. In five cases, the disease occurred as the result of the handling of rabbits killed in the woods near Dayton.

4. A thorough investigation of the incidence of this disease in Dayton prior to 1927, led to the discovery of 25 cases, dating back to 1908. All but 2 of these older cases occurred in market men. At least seven deaths, attributable directly to tularemia, have occurred in Dayton during the past decade.

5. In forty cases in the Dayton series, the disease was of the ulceroglandular type. Sporotrichosis-like nodular lymphangitis was present in 6 patients. In 9 cases, there was no primary ulcer, the organism having apparently passed through unbroken skin (glandular type). No example of the oculoglandular or typhoid types were encountered.

6. In every instance, the disease resulted from direct contact with the wild cottontail rabbit. East of the Mississippi River, the deer-fly and wood-tick do not play any important rôle as transmitters of the disease.

7. Up to May 1, 1928, reports of 613 authentic cases, including the series here reported, have come to the attention of Francis. Cases have been reported in every state of the Union, except the New England States, Delaware, Wisconsin, and Washington.

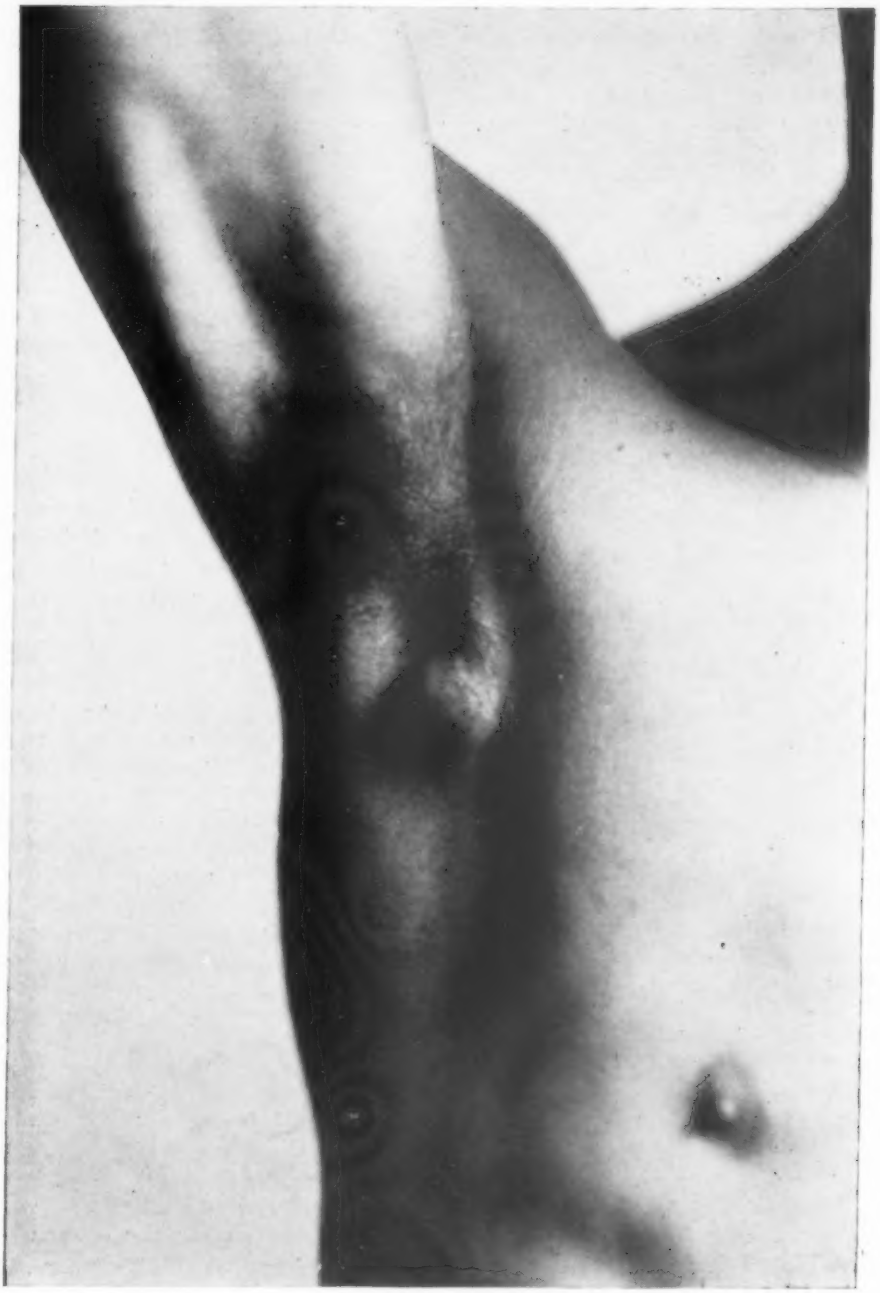

FIG. 20. Mr. A. L. G., case XXI. Right axillary adenopathy. Seven weeks after onset.

There have been 23 recorded deaths (3.7 per cent). With the exception of 3 cases occurring among laboratorians in England, and 7 in Japan, all of the cases have occurred in the United States.

8. The organism was recovered directly from human tissues in two cases. A human serum modification of Francis' cystine glucose meat infusion peptone agar was employed.

9. It was demonstrated experimentally that the organism will pass through the unbroken skin. The organism retains its virulence in guinea pig splenic tissue, preserved in glycerine in an ice-box, for two months.

10. The diseases known to ophthalmologists as Parinaud's disease and *conjunctivitis necroticans infectiosa* are clinically similar to *conjunctivitis tularensis.*

11. The diagnosis is usually simple if one has a suggestive history, together with an influenza-like onset (fever, chills and sweats, severe headache and aching sensations in the back and extremities, marked prostration) and the characteristic primary lesion and regional adenopathy. Confirmation is best obtained by specific agglutination tests at some laboratory provided with *Bacterium tularense* antigen. Material from the primary lesion or regional lymphnodes may be injected into a guinea pig or rabbit, and the organism recovered on special cystine-containing media.

12. There is no specific treatment. The treatment is essentially symptomatic. The primary lesion is a granuloma, and incision is distinctly contraindicated. Surgical drainage of the involved lymphnodes is indicated only when definite evidence of suppuration is present. The effect of immune serum on the course of the disease will be the subject of a further report.

NOTE:

The writer is deeply indebted to the physicians of Dayton for their enthusiastic cooperation; to Dr. Edward Francis, for his willingness to repeat and confirm the writer's findings, and for constant encouragement; to Dr. Aldred Scott Warthin, Director of the Pathological Laboratories of the University of Michigan, for the use of his photomicrographic apparatus; to Dr. Eli R. Crew, Superintendent of Miami Valley Hospital, for many material aids.

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Editorial

JOHN HUNTER, THE NATURALIST SURGEON

1728-1928

His Influence Upon Internal Medicine.

In the two hundred years that have passed since the birth of John Hunter the development of Medicine has reached such a stage in its evolution that the influence of this interesting individual upon that development can be more clearly seen and evaluated. He is ranked among the master minds of medicine. His name is linked with Harvey among the anatomists, and with Lister among the surgeons; and there is not a single field of practical medicine or surgery in which his name may not be mentioned as a great fore-runner. Yet, curiously enough, the reader of his life and works cannot confess to any feeling of attraction towards his personality—quite the opposite state is aroused. As a boy in the village of Long Calderwood near Glasgow his reactions were not regarded as becoming a Scots boy whose father came from an ancient line of gentry and whose brothers were preparing for careers in law and medicine. He was stupid in learning to read, idle and a cry-baby, a failure in the Latin School in which his brothers had been successful, and mother-spoiled. Surely today he would be rated very low in any intelligence test, and would be regarded with suspicion as to his future mental development. Even his relatives had no illusions as to his being a difficult child; but in their unprejudiced descriptions of him they mention several characteristics of saving-grace quality that serve to lessen the unpleasant impression his boyhood and early youth make upon us.

Although obstinate and rebellious as to book-learning, he was conceded to be observant, quick of perception and exceedingly neat of hand, particularly in anything of a mechanical nature. His own version of these unpleasant youthful years was "They wanted to make an old woman out of me, or that I should stuff Latin and Greek at the University; but these schemes I cracked like so many vermin as they came before me." Different indeed was he from his older and more attractive brother William, who also achieved lasting fame as a master in medicine. But the secret of John Hunter's apparent failure as a proper kind of a Scots boy was, as in the case of many another boy of many different periods in the world's history, that his heart's interest was *scientific*. He was born a *naturalist*, and a *naturalist* he remained all his days, and what he contributed to medicine and surgery was the result solely of this character of his intellectual make-up. He tells us later in his life, that as a boy he had the urge for an understanding of the natural world

about him, "the clouds, grasses, leaves, ants, birds, tadpoles and caddis-worms." He watched these and questioned people concerning them to no satisfaction. Books and book-learning he hated; to go bird's-nesting, to compare their eggs and note their differences in color, size and shape gave him his kind of mental satisfaction and discipline. It was but natural, therefore, that anatomy should attract him as he came to manhood's realization that there was work to be done in this world. So in September, 1748, he began work with his brother William in London, chiefly in the dissecting room, and in the second year became demonstrator to the students attending his brother's courses of lectures. John's life at this time showed that any charge of laziness made against him in early life was untrue, he slaved from morning to night in the most unpleasant business of the dissecting room of that period and its necessary relations with the resurrection men with whom he is said to have made great friends. Quite naturally the social amenities of such a life did little towards making a gentleman out of him, although his brother was given credit for making him a man. But circumstances brought him into contact with Cheselden during the summers of 1749 and 1750, and in the next year with Percivall Pott. From the former surely some refining influences must have touched Hunter, for Cheselden was noted for his refinement of manner and his love of art. Hunter's interest in pictures and prints in later life may possibly date back to his association with Cheselden. Nevertheless, Hunter's attitude towards the world, and particularly that of his own profession, savored of a contemptuous superiority; his conceit made him at times a most unlikable person, coarse and repulsive. If ever a human being was sold, body and soul, absolutely to his work that individual was John Hunter. His brother William was like him in this respect. Together they tore through life with untiring passion for scientific work, without other recreations or hobbies, putting only such value on the pecuniary rewards of practice as would enable them to obtain means whereby they could pursue their scientific passions. The results of this passion appear as an everlasting memorial in their individual and combined anatomical achievements. But the glory of all this accomplishment is tarnished by the controversies which the Hunter brothers carried out with the Monroes and Percivall Pott, and finally with each other, as was inevitable because of their natures. Work was the only bond between them; they would fight side by side against any outside claimant to their discoveries, and finally against each other when both claimed priority. All of this makes a sad story of the unpleasant aspects of human actions, even when viewed in the light of the controversial fashion of the times. The final estrangement of the brothers was their dispute over the discovery of the structure of the placenta and its communication with the uterus. No justifiable excuse or apology for their ugly quar-

rel has ever been shown, and the knowledge of it completely effaces any personal feeling of liking or admiration the reader of today might otherwise have incited within him by their other great qualities.

But it is neither a history of their lives and achievements nor an estimate of their personalities that I wish to present here. Rather is this brief sketch designed to illuminate the influence that John Hunter's life and works exerted upon the development of medicine. That this influence was a tremendous one is universally conceded We give him a position among the masters—the great masters—of medicine. As a philosopher he has even been compared with Shakespeare. He is perhaps most commonly thought of by the medical profession as a great surgeon, and was called by Abernethy the master-surgeon of all times. Yet an operating-surgeon he surely was not. Few operations are ascribed to him; and the only important one associated with his name is the tying of the femoral artery for popliteal aneurism which had not previously been done. This operation was approached by him, not from the operative standpoint, but from that of anatomy, physiology and pathology. Hunter himself had no high opinion of operative surgery; he considered an operation to be a reflection on the healing art and an acknowledgment of the insufficiency of surgery. In truth, as far as surgery is concerned, Hunter was a surgical-pathologist—a biological philosopher. His interest lay in the anatomico-physiological principles involved in any morbid condition rather than in the operative attack. The leading surgical consultant of his time, it is not known to what extent he operated upon the patients who came to him, or had others operate for him. He, himself, had a very definite dislike for the practical application of scientific knowledge. Practice was subordinate to anatomy and pathology. All that he received in fees he spent on scientific investigations and on his museum. The oft-quoted remark about that "damned guinea," reluctantly earned, only because he must have it to spend on his science, reveals the absorbing passion of his life. Even at the last, when his practice had become lucrative, he spent all on his work and left only his museum consisting of more than 13,000 specimens, for the support of his wife and children. The popular opinion of Hunter at the height of his fame is also revealing; he was regarded as a surgeon who would do everything to discover the nature of one's ailment, help it if it could be helped, but if not amenable to treatment, would do everything in the world to secure an autopsy on the patient. His museum or "Natural History" as he called it, was open to visitors two months in the year, October for the profession, May for "noblemen and gentlemen who were only in town during the spring." In every field of natural history, anatomy, physiology, pathology, anthropology, botany and geology he made discoveries of great importance and established new facts. For forty-five years of his life (1748-1793) he was engaged in "dogging the footsteps of Nature day by day" in order to spy out her secrets and to obtain for his mu-

seum any specimen that would throw light on the manner in which Nature defended living matter and repaired defects in living tissues. This was perhaps the keynote to his medical philosophy. He has often been called a "vitalistic" surgeon; he replaced the old surgical quackery and empiricism by the scientific method of observation and experiment. He was the first surgeon to make the actions and reactions of living tissues the foundation stone on which all surgical practice must be based. He was the first man of medicine to realize the unity of all living matter, and to assert that the study of the minutest forms of life would illuminate the more complex structures and functions of the human organism. Without the knowledge of the laws and conditions under which vital actions and reactions were originated and maintained the surgeon and the physician were pure opportunists, empirics or quacks. Hunter created thus a new epoch of medical philosophy; he laid the corner-stone of modern medicine. He saw clearly that disease was only altered life; he saw further that Nature attempted to return to normal life by resisting the causes of disease and repairing the damages resulting therefrom. He believed that all living matter possessed the power of defense and repair. Upon this he based his conception of the treatment and cure of disease; through observation he thought it possible to obtain a knowledge of natural defense and repair, and to apply these principles in the treatment of patients. This thought animated his entire life work, and was responsible for his collection of ten or more thousand specimens that to him threw light upon these natural laws in the multiform methods of Nature. In this museum he attempted to collect everything that would throw light upon the laws of growth and repair. Without knowing anything of the histological changes underlying inflammation, he regarded its varied manifestations as essentially curative in nature, and his recognition of this fact constitutes perhaps his most important contribution to the practical side of medicine. He was more than a century ahead of his times in this conception, as well as in many another one. If we read Hunter today with the modern understanding, and substitute the modern terminology of reflex, functional adaptation, hormone-reactions, toxic effects, anabolic, katabolic, etc., for his *consciousness," "sympathies," "morbid poisons," "combination," "decomposition,"* etc., we will be startled at their extremely modern quality. None of the discoveries in medicine made since his day puts him behind the times, for no matter what their interpretation may be at any period, the vital phenomena he saw and described will remain essentially the same. If we read Hunter's works with this spirit of insight we shall find that his observations threw new light on practically every organ and tissue of the animal organism. Our knowledge in many ways remains today where Hunter left it.

Hunter was not a scholar of his times; he knew no mathematics, no logic and was ignorant of the classics. How much better it would have been

for him and the world if he had added such erudition to his great store of intrinsic mental ability and energy. He was always handicapped by an inability to express his thoughts, and his written works suffered from this educational deficiency. He was born a genius possessing wonderful powers of observation, abstraction and analysis, and these qualities added to his insatiable love for work, his passion for original research, his indomitable will and his tremendous capacity for thinking made of Hunter the great philosopher of life and nature. He combined in an extraordinary degree the two philosophic methods of induction and deduction. In pathology particularly he employed the deductive method, reasoning from premises and hypotheses invented by himself. In spite of some errors the wonder is that so many of his speculative conclusions in physiology and pathology, made without the aid of microscope or chemistry, have been confirmed by later workers possessing this equipment. In deduction he often anticipated discoveries far beyond the facts at hand. Many examples of perfect induction are also found in his writings, but also others of fallacious reasoning by analogy and comparison. He used the inductive method chiefly in collecting and assembling the scattered facts of comparative anatomy and physiology, but much of his pathology was also based on induction. He employed the two methods, Deduction and Induction, at will, sometimes without fully coordinating the two methods, but this was only because, as has been expressed by Morris, that he, in spite of his wonderful genius, "fell short of being an absolute monarch of the whole kingdom of the intellect." Hunter has been criticized because of certain obscurities; Buckle explains these by saying that the conflict in Hunter's mind between Deduction and Induction darkened his understanding. Ottley laid them to deficient education. Morris explains Hunter's obscurities by the complexity of the subject or the fact that Hunter's own mind was in doubt. Be this as it may Hunter was stated by Buckle to have "remodelled the fabric of Knowledge;" he is placed with Harvey, Bacon and Newton as a man of science, and with Shakespeare as a man of natural genius. His contemporary and critic, Jesse Foot, however, asked scornfully: "What was John Hunter's service to Medicine and Surgery?" Arthur Keith has probably given the best answer to this question: "If I had to inscribe the tag attached to the coat lapel of the shade of John Hunter as it applied for entrance to the Valhalla of the great medical dead, I would write: 'This is the man who discovered that every measure to further healing and to preserve health and life must be based on an accurate knowledge of the vital processes of living flesh'." For this reason Hunter revolutionized medicine, and he did it as a philosopher of abnormal life—in other words as a pathologist and not as a practitioner.

Abstracts

Experimental Tularemia in Birds. By R. G. Green and E. M. Wade (Proc. Soc. f. Exper. Biol. and Med., May, 1928, Vol. XXV, No. 8, p. 637).

These investigators have previously reported that grouse are susceptible to experimental tularemia. Inoculation of an abrasion through the skin of a ruffed grouse results in a fatal septicemia. Preliminary experiments carried out on the susceptibility of the Hungarian partridge to experimental tularemia indicate that this bird is highly susceptible to the disease, a fatal infection resulting from an open inoculation of a skin abrasion. The pigeon appears to be relatively more resistant. In this bird an intramuscular injection causes the formation of a local lesion, and in some cases is followed by a generalized invasion by the organism. Even with the production of a septicemia, no clinical symptoms were observed in the pigeons in their series and those not killed have recovered. The ring-necked pheasant also appears to be relatively resistant to experimental tularemia. The domestic chicken appears to be absolutely resistant to the disease. Organisms injected intra-muscularly do not appear to invade and produce a general infection.

A New Liver Function Test. By Alice R. Bernheim (Proc. Soc. f. Exper. Biol. and Med., May, 1928, Vol. XXV, No. 8, p. 675).

A rise of the icterus index had been noted to occur folowing the intravenous injection of phenoltetrachlorphthalein. When bromsulphalein was used no rise in the index took place. At first the rise in index following the use of the phenoltetrachlorphthalein was thought to be its toxic action upon the liver. It was suggested by Dr. S. M. Bassett that, inasmuch as distilled water was used to dilute a 5 per cent to a 1 per cent solution in the case of phenoltetrachlorphthalein and no dilution was made in the case of bromsulphalein, the increase in icterus index might be due to the laking of red cells by the distilled water. Accordingly, injections of distilled water up to 100 cc. were given intravenously, and, as surmised, a rise in the icterus index was produced. From this observation the idea arose that this use of distilled water might serve as a liver function test. If the normal liver removes bilirubin from the blood, the source of bilirubin being the hemoglobin from destroyed red blood cells, it is reasonable to suppose that a disordered liver will remove it less efficiently. If, then in the normal person, after the injection of distilled water the icterus index rises from 2 to 4 points one-half hour after injection, with an average rise of 2.5 points and returns to its basal value in 5 hours, a greater increase in icterus index might conceivably be expected in the individual with a disordered liver, or the return to normal might be prolonged. Adequate dosage of the water was ascertained by experiment to be 25 cc. for individuals weighing from 100-110 pounds, with an increase of 5 cc. for every pound of body weight up to a maximum dosage of 50 cc. In the normal person results were obtained as stated. But contrary to expectations the injection of the water in abnormal cases occasioned either no rise in the index or a fall, according to the amount of dysfunction. The interpretation of these observations is at present wholly speculative. It seems unlikely that a disordered liver can more readily remove the bilirubin from the blood than a normal one. The results indicate that the test may be a measure of the bilirubin-forming, rather than of the bilirubin-removing function of the liver. Observations were carried out on 15 normal persons and on 112 hospital patients. The normal individuals

showed a rise of from 2 to 4 points in the icterus index. Of the hospital cases 28 showed either no rise or a fall. These 28 cases comprised: 5 of catarrhal jaundice, 1 of arsenical poisoning with jaundice, 2 of metastatic carcinoma of liver from primary in stomach, 5 of hepatic cirrhosis, 1 of cyst of liver, 1 of Wilson's disease, 1 of small liver with right lobe absent, 3 of carcinoma of head of pancreas, 3 of cardiac disease with decompensation, 4 of Hodgkin's disease, 2 of Graves' disease. The remaining 94 cases showed a rise in the icterus index. In 5 of these the diagnosis of liver disease was made: 2 cases with the clinical diagnosis of cirrhosis with ascites, 2 cases of enlarged liver in syphilitic patients, 1 case of localized carcinoma of liver, extension from gall bladder. Among these some indexes rose less than 2 points. Cases with the severest liver damage showed a fall in index, those with less damage showed no rise, and normal cases showed a rise of from 2 to 4 points. These facts make it seem possible that in some of the hospital cases showing a rise in index of less than the normal 2 points a corresponding slight liver dysfunction may be indicated. In 3 cases of thyroid disease (1 adenoma with symptoms of intoxication and 3 of Graves' disease) changes in the icterus index following the injection of distilled water corresponded to the rate of basal metabolism and the condition of the patient, the higher the metabolic rate, the lower the index. Bromsulphalein tests were made to check the water test. Where findings were normal in the dye test they were likewise normal in the water test. With the bromsulphalein test in jaundice there is always a 100 per cent retention of the dye one-half hour after injection irrespective of the severity of the liver involvement. With the water test the index either does not change or decreases according to the extent of damage. This test is accordingly a more delicate gauge of disturbance than the dye test, when jaundice is present. There is a fairly common impression that the intravenous injection of distilled water may produce unpleasant consequences varying from a mild chill to death. In none of these cases were there any unpleasant reactions. On the contrary restless patients were quieted, and all without exception experienced a feeling of well-being lasting several hours.

Effect of Liver Extract on Erythrocytes and Reticulocytes in Normal Individuals. By C. H. Watkins, R. Johnson and Hilding Berglund (Proc. Soc. Exper. Biol. and Med., May, 1928, Vol. XXV, No, 8, p. 720).

The effect of liver extract in pernicious anemia may be analyzed from the point of view of the immediate reaction, as well as of the sustained reaction. The immediate reaction includes among other things three distinct morphological features: the normoblastic response, the reticulocyte response and the liberation of the mature erythrocytes. It is a well-established fact that the bone marrow in pernicious anemia is hyperplastic and contains large numbers of erythrocytes in various stages of development. In other words, there appears to be a difficulty in the maturation of the erythrocytes necessary for their discharge from the marrow into the circulation. This faulty maturation is in character probably morphological rather than chemical, for the cells in the marrow are completely filled with hemoglobin and products of hemoglobin have been deposited in the various tissues, Thus the hemosiderosis, in the classical interpretation of pernicious anemia looked upon as a proof of the hemolytic character of the disease, might indicate a destruction of erythrocytes in the foci where they were formed before they were ever delivered into the circulating blood. When liver therapy is instituted, the bone marrow presumably is stimulated to mature and release the cells. A slight retardation in the maturation as compared with the discharge explains the three morphologic features of the immediate reaction. The effects of liver extract upon six normal individuals were studied for a period of ten days during which they were given 3 vials of liver extract (Lilly 343) or the equivalent of 300 gm, of raw liver daily. Their erythrocyte counts were between 4,500,000 and 5,800,000. Daily erythrocyte and reticulocyte counts

were obtained. That the results might be reduced to a common base line, the original erythrocyte count of each individual was called 100 per cent, and the subsequent increase or decrease in erythrocytes was calculated in terms of the per cent of the original value. In all cases but one there was a definite increase in erythrocytes at the 10th day. The percentage is an irregular curve up to the value of 120.7 per cent on the 10th day. The irregularity of the curve may be due to an attempt of the body to overcome the polycythemia. In clear contra-distinction to the occurrences in pernicious anemia no increase in the reticulocytes took place in the normal individuals, the percentage remaining between 0.0 and 2.0 per cent. There was no change in the leukocyte counts. The hemoglobin followed the red count, but probably not in full proportion to the increase in red cells. In all cases the individuals developed some symptoms of polycythemia vera; thus varying degrees of headaches, epistaxis, acrocyanosis and abdominal distress, were encountered. Attention is called to the immediate response in the normal individual as compared with the delayed discharge of mature red cells in pernicious anemia. If in pernicious anemia we base our comparison on the occurrence of increased number of normoblasts, the first signs of response to the liver come as early in one group as in the other. Thus the liver extract in normal individuals as in pernicious anemia brings about an immediate release of red blood cells into the circulating blood. In the normal individual the maturation of the cells is complete and the release rapid; in pernicious anemia the maturation is retarded, discharge of incompletely matured cells occurs and precedes the discharge of fully matured ones; the process as a whole is prolonged.

Hemoglobin Construction within the Body as Influenced by Diet Factors. A Consideration of Anemia Problems. By G. H. Whipple (Am. Jour. of Med. Sc., June, 1928, CLXXV, No. 6, p. 721).

Whipple is convinced that a wrong assumption has seriously hampered the study of certain human anemias. Attention has been focussed upon hypothetical toxins which were supposed to destroy red cells *in vivo* and thus bring about the anemia. Because it can be demonstrated that a few types of anemia were due to toxic or parasitic destruction of red cells (septicemia, drugs, malaria) it has been assumed that all other forms of anemia must be due to some hemolytic toxin produced in the intestinal tract, kidneys, tumor growths, etc. This idea is given up with great difficulty. Pernicious anemia is the stronghold of those who believe in toxic red cell destruction as the essential etiologic factor. The anemia associated with bothriocephalus infections, which is often called pernicious anemia, has long been cited as the real proof of the toxic etiology of pernicious anemia. Meulengracht reviewing all of the known facts could find no direct evidence for any demonstrable toxic substance in the bothriocephalus anemias, although he concludes that pernicious anemia is due to an obscure intestinal intoxication. Nevertheless, each one of his deductions may be used as an argument in favor of the theory that pernicious anemia is a *deficiency* disease. Whipple in 1922 advanced the view that in pernicious anemia there is a *lack* of stroma building material but a great excess of pigment and pigment building material. The important observations of Minot and his collaborators may be interpreted as evidence in favor of a *lack* of a stroma-producing substance so that pernicious anemia may prove to be a *deficiency* disease. It is difficult to reconcile the prompt remission in pernicious anemia due to liver feeding with a causative agent in the form of an intestinal toxin. It will be profitable to reëxamine all of the anemias and search for a possible deficiency factor rather than for an elusive toxin. It is permissible to assume that in the anemia of cancer cachexia we are dealing with a hemoglobin building material which is perhaps used up by the more vigorous and rapidly growing tumor cells. In the case of intestinal stricture or general malnutrition there may be a severe anemia due to lack of materials unabsorbed from the intestinal tract. The anemia of nephritis may

be explained as due to faulty conservation of hemoglobin building material. The normal kidney plays a part in the conservation of pigment material, and it may be assumed that the diseased kidneys fail in this function is in other excretory ones. It may be accepted as established that simple anemias due to loss of blood can best be treated by means of diet therapy. Pernicious anemia has been shown to be amenable to diet. Why not examine other obscure anemias and marrow diseases for a possible deficiency factor?

The Blood Pressure in Pernicious Anemia. By J. Lerman and J. H. Means (Amer. Jour. Med. Sc., June, 1928, Vol. CLXXV, No. 6, p. 777).

It is generally recognized that blood pressure is low in pernicious anemia, but the literature contains no adequate statistical study of the subject. Text-book articles on pernicious anemia usually state that the pressure is "low" or "very low." The present study is based on the blood pressure findings in 500 consecutive cases of pernicious anemia from the Massachusetts General and Peter Bent Brigham Hospitals. The observations were all made with the patient in bed by the the auscultatory method of Korotkoff. Analysis of the observations made showed only slight variations in the averages due to age or sex. Compared with the average figures for normal people the blood pressure is significantly lower in pernicious anemia. The incidence of systolic hypotension in controls varied from two to three per cent, and of diastolic from 0.3 to 1.6 per cent. In the pernicious anemia series the incidence was about 11 per cent for systolic and about 30 per cent for diastolic hypotension. These percentages corrected for the age distributions of the controls are still higher. Hypotension is a more frequent condition in pernicious anemia than in tuberculosis. It appears that in pernicious anemia hypotension is associated with an almost complete disappearance of hypertension whereas in tuberculosis patients the existence of hypotension has but little effect on the frequency of hypertension. The infrequency of hypertension in pernicious anemia is of distinct interest, being practically as rare as is the presence of free hydrochloric acid in the gastric juice. Until further control data on the anemia have been sceured no diagnostic weight can be laid on blood pressure. The pulse pressures in pernicious anemia are higher than the corresponding normal ones by 9 to 17 mm. of Hg. This increased pulse pressure is apparently a feature of an increased volume flow of blood of a compensatory nature, and finally results in hypertrophy of the cardiac musculature. With improvement in blood picture the pulse pressure tends to diminish.

Reviews

Clinical Laboratory Procedures. By George L. Rhodenburg, M. D., Director of Laboratories, Lenox Hill Hospital; Consulting Pathologist, Lincoln Hospital, Misericordia Hospital, Beth David Hospital, New York. 266 pages. The MacMillan Company, New York, 1927. Price in Cloth, $3.25.

This is a collection of laboratory methods which in the hands of the writer have shown their relative simplicity and clinical accuracy over a period of years of actual use. Where several methods are known or in common use, the one which practical experience has indicated, for one or another reason to be preferred, has been arbitrarily selected. Some knowledge of laboratory procedure on the part of those using the volume is pre-supposed. No claim is made for originality, and free use has been made of all current text-books. An effort has been made to present concisely such procedures as are frequently undertaken in routine work. No attempt has been made to discuss the value of a given procedure, or to furnish a bibliography. The volume bears out the modest statements of the preface. The most important and most frequently used laboratory procedures in clinical diagnosis are given in simple concise form and the whole represents a well-chosen collection. They are given in sufficient detail to be usable by the student or laboratory assistant who possesses ordinary laboratory initiative and experience. The book is interpaged with blank leaves for additional notes or new methods. It is a handy and convenient little manual for the clinical laboratory and will be found very useful there.

The Examination of Patients. By Nellis B. Foster, M. D., Associate Physician to the New York Hospital; Associate Professor of Medicine at Cornell University College of Medicine. Second Edition, Revised. 392 pages, 83 figures, partly in color. W. B. Saunders Company, Philadelphia and London, 1928. Price in cloth, $4.50.

The first edition printed in 1923 was reprinted in January and April, 1924, and in September, 1925. It was written in the belief that it would be of help to the practitioner of medicine, its aim being to present as clearly and concisely as possible the methods on which accurate diagnosis rests. The author's experience in hospital and private practice impressed him with the need for such a book as an intermediary between the classical descriptions of the text-books of medicine and the treatise on the latest modes of treatment. Refinement of diagnosis compels the use of the trained senses of touch, sight and hearing, but it is certain that the modern development of laboratory methods and the over-exploitation of the clinical laboratory have diverted attention from these most important fundamentals. While this fact may be realized by the physician whose professional activities are confined to hospitals, its realization is not general. Rarely does the laboratory test alone reveal the nature of disease; it is usually only a support to other evidence which must be obtained in other ways, from the clinical features chiefly. Clinical medicine rests upon accurate diagnosis. This fact is being recognized today as never before. The treatment of symptoms is, in any major sense, an aberration that has vanished. The ability to seize on the relevant facts out of a mass of data is the mark of the true clinician, and this applies both to the knowledge of pathological details and the clinical features. While the knowledge of the former has been extended in a marvelous degree, the clinical features, on which the differential diagnosis of one disease from another

depend, are relatively few in number. The first edition brought to the author many letters from physicians acknowledging the practical help derived from it and requesting that the subject of differential diagnosis be attempted in the same concise way as that employed in describing methods of examination. This the author has attempted in this book, with some misgivings on his part. The examination of the book shows, however, that these were not justified; and the reviewer regards this volume as one of the most useful that could be placed in the hands of the medical student or practitioner. It represents an exposition of the highest type of medical practice—technical proficiency, accuracy of observation, and knowledge in the assembling and interpretation of the data secured. Diagnosis is a science and an art; a science in the method of using facts secured, and an art largely in the mode of collecting the facts. There are many sources of error in diagnosis, such as errors of judgment, errors in analysis, errors in data, but the commonest of all are errors in technique. Technique in music produces beauty of tones; in medicine it secures accuracy of data. This book then is an argument for perfection of technique in diagnosis, and is such we recommend it in the highest terms of approval.

Text-Book of Clinical Neurology. By Israel S. Wechsler, M. D., Assistant Professor of Clinical Neurology, Columbia University, New York; Attending Neurologist, The Montefiore Hospital, New York. 725 pages, 127 illustrations, octavo volume, W. B. Saunders Company, Philadelphia and London, 1927. Cloth, $7.00.

The object of the author has been to give a digest of what is known in neurology without stressing polemic material or detailing case reports. References to literature have been more or less consistently omitted from the text. The work is based mainly on personal teaching and clinical experience, and, therefore, represents in a great measure an individual approach to bedside neurology. The author hopes that the personal touch will make up for many of its omissions and defects. For the benefit of those who would pursue the subject farther the author has given at the end of each chapter a few of the more useful references bearing on the topics discussed. In doing this he has made an effort to separate the wheat from the chaff. He has also departed from the customary practice of illustrating the text with numerous photographs of patients, and has relied more on reproductions of pathological specimens and anatomical drawings which permit of the interpretation of signs and symptoms and lend understanding to the clinical manifestations. As the book is essentially one of clinical neurology, he has attempted to present, wherever possible, the various diseases in such a way that the signs and symptoms grow out, as it were, of the anatomico-pathological substratum and are seen to be consequent upon the underlying physiological disturbance. The anatomical and pathological facts on which the subsequent description of the clinical entity, its development and course is based, are outlined in brief, concise paragraphs. The author has also been wise in omitting the customary introductory chapters on anatomy and physiology, for unless they actually form part of each disease entity they have no place in a clinical neurology. No student expects to learn anatomy or physiology from a textbook of neurology. Of all the branches of medicine, clinical neurology lends itself best to the interpretation of signs and symptoms in terms of disease structure and function. The modern tendency in neurological diagnosis is to weave anatomy, physiology, pathology and symptomatology into one pattern. Because of the inevitable overlapping the classification of neurological diseases offers many difficulties, and it is difficult to be consistent in following either a pathological, anatomical or clinical classification. The author has adhered roughly to the nosology based on the last two, and has adopted the order followed by Oppenheim. The field of nervous disease has grown so vast that it is practically impossible, except in an encyclopedic work, to gather everything between the two covers of the volume. Wechsler has, therefore, omitted consider-

ation of most of the diseases of the ductless glands usually included under neurology, since they are more properly placed under general and experimental medicine. He discusses them only in so far as a given endoctrine disturbance has any direct neurological implication. Part I consists of a very complete exposition of the "Method of Examination;" diseases of the spinal cord are discussed in Part II; the peripheral nerves in Part III; the brain in Part IV; and the neuroses in Part V. The various diseases of those structures are discussed in a clear and concise style, which tends to give them an individuality that is so often lacking in the text-book descriptions of diseases of the nervous system. For that reason this text-book should have an especial value for the medical student, who is, so often, discouraged by what seems to be hopeless confusion as far as the differentiation of nervous affections is concerned. Essential points of knowledge only are given, and unsettled matters are only very briefly discussed as to the main points in question. The illustrations serve their purpose very well. A large amount of good common sense is scattered through the pages of the book; and the paragraphs on treatment are unusually free from fads. Psycho-analysis is given no more than its proper consideration. On the whole this work has much to commend it as a text-book.

The New York Academy of Medicine Lectures on Medicine and Surgery. First Series, 1927, 319 pages, 39 illustrations. Paul Hoeber, Inc., New York, 1928. Price in cloth, $5.00.

The first series of Practical Lectures for the general practitioner arranged by the Committee on Medical Education and given at the New York Academy of Medicine in 1926-27 met with such favor that the lectures are now published in book form in the belief that they will meet a need which is felt by the profession generally. The volume consists of fifteen lectures delivered by the following: Harlow Brooks, John F. Erdmann, John E. Jennings, S. J. Kopetzky, E. Libman, G. M. MacKee, J A. Alexander, L. K. Neff, J. O. Polak, H. Pool, David Riesman, M. G. Schlapp, J. M. Wheeler, H. B. Wilcox, and S. W. Wynne. In the order of lecturers named the subjects of the lectures were respectively, as follows: The Treatment of Cardiovascular Syphilis, Intestinal Obstruction, Surgical Aspects of Medical Conditions, Clinical Aspects of Common Otological Infections, General Infections by Bacteria, The Cutaneous Manifestations of Syphilis, Climate in Tuberculosis, Useful Drugs in Clinical Practice, Obstetrical Problems in General Practice, Surgical Aspects of Diseases of the Thyroid, The Treatment of Pneumonia, Pathological Causes of Human Misconduct, Remarks on Eye Conditions, Problems of the Child's First Year and Contagious Diseases. This group of interesting subjects receives individual and original treatment in the hands of these well-known medical writers. Brook's article on the treatment of cardiovascular syphilis in its therapeutic optimism will be of the greatest significance to the practitioner in the numerous suggestions contained within it. Erdmann's article on Intestinal Obstruction is of great practical value; the etiology and symptomatelogy are concisely given and the suggestions for treatment most sensible and practical. Likewise, the articles on the Surgical Aspects of Medical Conditions and the Clinical Aspects of Common Otological Infections contain many valuable hints and suggestions for the internist.

All the articles are all far superior to the average medical journal article. They have an individual and original point of view, based upon extensive or unusual clinical experiences, and contain much valuable clinical knowledge not to be found in any textbook. While the style of the different articles varies considerably they are all interestingly written, and such cannot be said of some of the volumes of lectures that it is now the fashion for hospitals and clinics to publish. This series, however, is of real practical value to the internist, and may be recommended for such as collateral reading. The book is printed in the usual good style and manner characteristic of Hoeber productions. The illustrations, particularly those in McKee's article on the cutaneous manifestations of syphilis, are very good.

Brain Abscess. Its Surgical Pathology and Operative Technic. By Wells P. Eagleton, M.D., Newark, N. J. Medical Director, Newark Eye and Ear Infirmary, Newark, N. J.; Chief of the Division of Head Surgery, Newark City Hospital; Attending Craniologist, Newark Presbyterian Hospital; Consulting Craniologist, St. Barnabas Hospital and St. Michael's Hospital, Newark, N. J., Muhlenberg Hospital, Plainfield, N. J., Mountainside Hospital, Montclair, N. J.; Chief of the Section of Surgery of Head, Base Hospital, Camp Dix, N. J., 1917-18. 297 pages, 40 illustration. The MacMillan Company, New York, 1922. Price in cloth, $7.00.

This monograph is the result of considerable intradural experience combined with animal experimentation and postmortem studies . Realizing that surgical as well as pathological and diagnostic information may be obtained from postmortems the author invariably made a personal effort to obtain an autopsy on all cerebral cases coming under his observation, and was fortunate in missing this in very few of the fatal cases previously examined or operated upon. Surgically considered intracerebral abscess stands in a class by itself, the problems presented in its surgical treatment differing from those of suppuration in other parts of the body and distinct from these encountered in the treatment of non-suppurative lesions of the brain. As many of the technical problems presented still remain far from solution the author calls attention to the unique physiological factors and pathological changes presented within the dura, and to the technique which in the author's opinion, most satisfactorily meets them. The success of intradural surgery always will depend upon utilizing every advantage offered by the preventive and reactive efforts of nature, while a single technical error may mean the loss of the patient's life, or at least of his subsequent usefulness. Cushing's technique has been largely used by the author in operating for intracranial suppuration. The writer attempts to correlate the surgical treatment of the different pathological lesions of brain abscess, since if even a moderate degree of success is to be achieved in the treatment of brain abscess, the surgical manipulation in each individual case must be adapted to the exact pathological lesion present. With this object in view emphasis is laid upon the pathology and on mechanical changes and a classification is adopted which is capable of individual clinical recognition, because the author believes that our present knowledge should enable us not only confidently to diagnose the presence of brain abscess, but also in a large proportion of cases to determine its location and whether or not it is surrounded by a capsule. To accomplish this the surgeon must divest himself of certain ideas inherent in the old classification of aural and nasal origins, and must conceive of them not according to their immediate origin, but pathologically, according to the causative lesion of entrance into the central nervous system; that is, whether by extension by direct tissue suppuration or by retrograde thrombophlebitis, for which the author suggests the terms *Adjacent* (*Secondary*), and *Intercurrent* (*Tertiary*), when immediately occasioned by a secondary gross lesion such as sinus thrombosis, to differentiate both from abscesses originating from bacteria circulating free in the blood stream, the latter being pathologically *metastatic*, even though the original focus of infection may be in the ear or the nose . The author states that one of the chief objects of this work is to enable the surgeon to approach the treatment of brain abscess in a pathological as well as a technical mental attitude. The book has naturally a strong personal character, since it is largely an account of experience in more than fifty cases of adjacent brain abscess that have come under the writer's observation. The book was written because the author recognizes that many deaths might have been avoided had he earlier been in possession of the knowledge gained by his failures, and which he now offers here for the aid of others. Case histories are given in detail, and technique is minutely described. Altogether it is a very complete monograph upon the subject, and of great value from the diagnostic side, as well as from the operative. The case histories, in themselves, are most instructive. The abstracts of the reported cases of brain abscess given in the Appendices are also valuable in assisting the reader to the fullest possible grasp of this subject.

College News Notes

DR. SMITHIES HONORED BY THE BOARD OF GOVERNORS

The following is a resolution of the Board of Governors, adopted at their meeting on March 9, at the close of the Twelfth Annual Clinical Session:

"In recognition of the earnest, untiring, and faithful service of our retiring President, Frank Smithies, in the upbuilding and maintenance of The American College of Physicians, be it resolved that the Board of Governors accord to him its hearty vote of appreciation, thanks, and commendation. And be it further

"Resolved that this resolution be spread upon the Minutes of this meeting of the Board of Governors, and that a copy be sent to Dr. Smithies."

To all who are familiar with the history of the development of the College of Physicians the recognition of the part played by Dr. Smithies as expressed in the above resolution of the Board of Governors will seem but a slight acknowledgment of the great service rendered by the late President. Dr. Smithies rescued the College from an early death and through his great exertions saved the frail organization, and in the years that followed built it up into the successful institution that now without any doubt is destined to become a leading force in the growth and progress of internal medicine in the United States. This great work was accomplished in the face of the most bitter opposition and the early days of the College's growth were beset by many difficulties which were successfully surmounted through his untiring zeal and tremendous efforts. That the College was actually created by him and made what it is today through his work must be acknowledged by those who follow him, and it is fitting that those who now take up the guidance of the policies of the College bear this fact in mind with gratitude and render him due credit for his great service. From him they can doubtless obtain most valuable advice in the consideration and settlement of the problems that must still be worked out in order to make of the College a more helpful instrument in the development of American Medicine. From all quarters Fellows of the College have expressed their desire that he will still continue to take an active interest in the affairs of the College.

DR. OTIS HONORED

Dr. Edward O. Otis, F. A. C. P., of Boston, was recently honored by a dinner of a large number of physicians and friends at the University Club. This celebration marked the completion of forty-two years of service by Dr. Otis on the staff of the Boston Dispensary, having been first appointed in 1886. He was presented with a humidor with an engraved silver plate. Dr. Otis who is now eighty years of age graduated from Harvard Medical School in 1877, and has received the degree of Doctor of Science from the University of New Hampshire and Tufts College. He did postgraduate work abroad, and has established an international reputation in the field of Tuberculosis. He is an ex-president of the National Tuberculosis Association and of the American Climatological and Clinical Association,

is a member of the American Public Health Association, the American Medical Association, and his county and state associations. He has served as a member of the Board of Governors of The American College of Physicians to represent his State for some years.

Col. Bailey K. Ashford, F. A. C. P., recently retired from active service in the Medical Corps of the United States Army and located in San Juan, Porto Rico, was recently appointed by the Government of Porto Rico as its representative to the International Congress on Tropical Medicine and Hygiene to be held at Cairo, Egypt.

Dr. Jonathan C. Meakins (Fellow), Montreal, was elected President of The American Society for Clinical Investigation at Washington, D. C. on April 30.

Dr. Kenneth M. Lynch (Fellow), Charleston, S. C., and Dr. Sidney K. Simon (Fellow), New Orleans, La., were elected Vice-Presidents of The American Society of Tropical Medical at Washington, D. C. on May 2.

DR. WARTHIN HONORED IN INDIANA UNIVERSITY

Dr. Aldred Scott Warthin, director of the department of pathology in the medical school of the University of Michigan, was awarded an honorary doctor of laws by Indiana University at commencement Monday, June 11, with the following citation:

"In recognition of your achievements as teacher, author, editor, physician, as director of the pathological laboratory at the University of Michigan for 25 years, and as an investigator in the field of pathology, on recommendation of the board of trustees, I take pleasure in conferring upon you, an alumnus of Indiana University, the degree of Doctor of Laws.

Dr. Bernard L. Wyatt, F. A. C. P., Medical Director of the Desert Sanatorium of Southern Arizona at Tucson, has been appointed Director of an Institute of Research to study the nature of solar radiations and their effects on living matter. The Board of Directors of the Desert Sanatorium has appropriated $250,000.00 for this study.

Dr. Solomon Solis-Cohen, F. A. C .P., of Philadelphia, has been made the Medical Director of the Jewish Convalescent Home at Willow Grove, Pa.

Dr. Tom Bently Throckmorton (Fellow), of Des Moines, Iowa, was re-elected during May as Secretary of the Iowa State Medical Society.

Colonel Bailey K. Ashford (Fellow) after many years of distinguished service in the United States Army Medical Corps retired on February 11. From 1913 to time of retirement, he was President of the Board to Study Tropical Diseases, U. S. Army, and has been stationed in Porto Rico. Since 1925, he has been a member of the Committee on Tropical Research of the National Research Council, and since 1926, has had the appointment of Professor of Tropical Medicine and Mycology at the College of Physicians and Surgeons, Columbia University, New York City. He is a Fellow of the American Medical Association, an ex-President of the American Society of Parasitologists, an ex-President of the American Society of Tropical Medicine, a member of the Association of American Physicians, and a member of the Association of Military Surgeons of the United States.

Dr. Stuart Graves, F. A. C. P., now Dean of the University of Louisville, School of Medicine, has been appointed Dean of the School of Medicine of the University of Alabama, beginning with the fall semester, to succeed Dr. Clyde Brooks who will act as Chairman of a newly created Faculty Committee on Research. The School of Medicine of the University of Alabama is preparing a program for a four year medical course, and Dr. Graves, Dr. Samuel W. Welch, F. A. C. P., State Health Officer, and Dr James S McLester, F. A. C. P., Professor of Medicine, and President Denny of the University will constitute a special advisory council to consummate the plans for the course. An extensive study of the best medical schools and teaching hospitals will be made. The plan contemplates the appointment of full-time teachers in the major branches, establishment of a hospital, nurses training school, etc.

OBITUARY

George Nicholas Acker, 2nd, M.D. (Associate, February 20, 1924; Died, February 27, 1928.)

Doctor Acker was born in Washington, D. C., August 2nd, 1888. After his attendance in preparatory school he entered Gettysburg College, Pennsylvania, from which institution he was graduated. Later he entered the medical department of the College of Physicians and Surgeons, Columbia University, New York City, from which institution he was graduated in 1914. After his graduation he did hospital work in New York City. He obtained his internship in St. Luke's Hospital in which institution he served from June 1914 to January 1916. In 1916 he received an appointment as resident physician in St. Luke's Hospital. Later he served as instructor in the Department of Clinical Medicine of his Alma Mater and was for a short time an assistant to Dr. Lambert.

At the outbreak of hostilities he entered the United States Army Medical Corps, serving for two years and four months, reaching the grade of Captain. He was a member of the Stewart Walcott Post of the American Legion, the Veterans of Foreign Wars, and the Military Order of the World War.

After the War he established himself in the City of Washington where his Uncle, the late George Nicholas Acker, Professor of Pediatrics at George Washington University Medical School, one of the early members of the American Pediatric Society, had long been established in practice. Doctor Acker not only was the namesake of his distinguished Uncle but he seemed early to exhibit many of the qualities shown in the long fruitful life of his Uncle.

In establishing himself in practice he was appointed an Associate in Medicine at George Washington University, being in charge of the Department of Physical Diagnosis. He was instructor in Clinical Medicine in this institution at the time of his death, which occurred February 27th, 1928.

Doctor Acker was a member of the American Medical Association, The Medical Society of the District of Columbia, The Medical Society of the George Washington University, The Southern Medical Society, The Medical Society of Maryland, and The Medical Society of Virginia. He also held membership in the American College of Physicians and the Clinico-Pathological Society.

He was a member of the Garfield, Childrens' and Emergency Hospital Staffs.

Doctor Acker's inherent thoughtfulness and courtesy toward all, together with his skill as a physician, soon built for him a large clientele. It is to be regretted that such a promising professional career would be so abruptly ended. To quote from an obituary written by one of his intimate friends—"He bubbled with the sort of humor that chases gloom to its hiding place and leaves no wound. His wit was always kind. He refreshed the sick and weary soul like a Summer shower and hatred had no companionship with him."

At his death the profession lost a great physician—humanity a friend.

Doctor Acker was buried in Arlington National Cemetery.

Vth INTERNATIONAL MEDICAL CONGRESS FOR INDUSTRIAL ACCIDENTS AND OCCUPATIONAL DISEASES, BUDAPEST, 1928

In accordance with a resolution of the "Permanent International Committee", the Vth International Medical Congress for Industrial Accidents and Occupational Diseases will be held in Budapest, Hungary, September 2nd to 8th, 1928.

All those who are engaged in the subjects to be discussed, are cordially invited to attend.

Budapest, 12th March 1928.

Prof. TIBERIUS GYORY
Under Secretary of State,
Chairman of the Organization Committee.

Prof. TIBERIUS VEREBELY
Professor at the Pazmany Peter University of Budapest, Chairman of the Executive Committee.

An Advertising Policy

The Board of Regents of The American College of Physicians, official publishers of ANNALS OF INTERNAL MEDICINE, have authorized and initiated a policy for the acceptance of suitable advertisements in this Journal. Publishers of high-grade medical books and manufacturers of the most reputable instruments and therapeutic products will find this Journal an advertising medium for reaching the preferred class of internists. There is no intention of making this a commercial journal or of infringing upon its past policy of dignity and conservatism.

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